Structural alterations in schizophrenia : relationship to cognitive deficits and drug response

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Structural Alterations in Schizophrenia: Relationship to Cognitive Deficits and ~~Treatment Response~~ DRUG RESPONSE.

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To Galina and Marc

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Abstract

INTRODUCTION: First, the region of interest (ROI) studies identified diffuse as well as circumscribed structural brain alterations in schizophrenia. However, ROI method has a number of limitations that are surpassed by a recent development in automatic structural image processing, voxel-based morphometry (VBM). The main advantage of VBM is that it allows identification of structural alterations throughout the entire brain. Second, structural alterations in schizophrenia have been found to be associated with cognitive deficits by ROI studies. Moreover, ROI studies noted differences in structure/neurocognition relationship between schizophrenia patients and normal controls. However, there was no previous investigation of the association between VBM identified alterations and cognitive deficits using a comprehensive neuropsychological assessment, and no formal testing of the possible alteration in structure/function relationship in schizophrenia. Third, cognitive deficits are gaining priority as a target for treatment, since they are better predictors of functional outcome than symptomatology. Novel or atypical antipsychotics have greater efficacy over conventional antipsychotics in improving cognitive functioning in schizophrenia. The structural predictors of atypical antipsychotic drug response in terms of cognitive functioning, however, were not previously investigated. AIMS: The thesis aims were: i) to identify the pattern of structural alterations in schizophrenia patients (n = 47) relative to normal controls (n = 45), utilising VBM technique (Study 1); ii) to characterise the pattern of cognitive deficits in the present cohort (Study 2); iii) to investigate the structure/neurocognition relationships in patients, contrasting them with those of controls (Study 3); and iv) to explore the predictive value of structural alterations to the 6-week treatment response with atypical antipsychotics as assessed with neurocognitive measures (Study 4). RESULTS: The patients showed a significant reduction in global grey-, white-, and total brain volumes, as well as localised alterations specific to the left hemisphere, including grey matter reductions in the inferior frontal gyrus (IFG), superior temporal gyrus and lingual gyrus, white matter reductions in the posterior and occipital lobes, and grey matter increases in the putamen and the precuneus (Study 1). Cognitive deficits were observed on all measures, with the most pronounced deficits in the domains requiring verbal function, including verbal memory and learning, verbal fluency, and verbal working memory (Study 2). Reduction in global brain tissue was associated with the lower general intellectual ability and cognitive deficits that were found to be dependent on IQ, whereas local structural alterations were associated with specific cognitive deficits in schizophrenia patients (Study 3). The structure/neurocognition relationships that dissociated patients and controls most clearly were between verbal memory and larger IFG volume in controls but larger volume of the precuneus in patients. Larger precuneus in patients was also associated with more recurrent form of the illness (Study 1). Further, verbal memory and learning, verbal working memory and dexterity showed clear improvement after 6 weeks of treatment with atypical antipsychotics, which could not be attributed to the practice effect (Study 4). Greater

improvement in verbal memory and learning was predicted by *smaller* volume of the IFG and precuneus (Study 4). CONCLUSIONS: The present cohort of schizophrenia patients is characterised by the structural alterations specific to the language dominant hemisphere and the corresponding differential cognitive deficits of language dependent functions. The pattern of structure/neurocognition associations implicates a greater significance of a posterior brain area, the precuneus, in memory function in patients, which might be related to the pathogenesis and the course of schizophrenia. Furthermore, poorer memory at the baseline and an improvement in immediate verbal memory following the atypical antipsychotic treatment in patients with 'normal' precuneus suggests that the increased precuneus might play a compensatory role in memory function. Overall, the findings highlight the emerging role of the precuneus in the course, cognitive functioning, and treatment response in schizophrenia and press the need for further studies with concurrent use of multiple structural and functional MRI techniques to obtain a better understanding of brain structure-function relationships in this population.

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PREFACE

MRI-BASED VOLUMETRICS AND SCHIZOPHRENIA

Magnetic Resonance Imaging (MRI)-based brain volumetrics is an established domain of brain science, which has been applied to understanding developmental changes in the brain (e.g. Giedd et al., 1996; Caviness et al., 1996; Huppi et al., 1998), recognition of neurodegenerative diseases (e.g. Jernigan et al., 1991; Aylward et al., 1994; Mori et al., 1997), and has substantially contributed to the search for structural correlates of disorders with uncertain pathogenesis, such as schizophrenia (e.g. Andreasen et al., 1986; Suddath et al., 1989; Wilke et al., 2001).

The theoretical foundation underlying the proposition that brain volumetrics is usefully pursued as a science is based on both theoretical and observational thesis that volume is an evolutionarily and developmentally regulated fundamental property of brain tissue and its structures (e.g. Armstrong, 1983; Ringo, 1991). The volume of a neural structure is the direct reflection of its size, shape, as well as the pattern of arrangement and densities of its cellular components (Caviness et al., 1999). Consequently and plausibly, the volume is thought to relate in some regular way to the information processing capacity of the structure. The optimum information processing capacity of the structural component will relate in some regular way to its volume relative to that of other brain components of the distributed neural system. From the evolutionary perspective, the volume of the brain and its components will reflect its optimisation within the framework of constraints imposed by body anatomy and physiology (Gerhart and Kirschner, 1997). From the ontogenetic perspective, the volume of the brain and its components will be relatively uniform among individuals of species, reflecting the constraints of cell and molecular biological processes, dominated by cell internal controls and modulated by cell external mechanisms (Caviness et al., 1999). In the

neuropathological conditions, such as schizophrenia, the neurodevelopmental and/or neurodegenerative processes affecting the cells will reflect on the volume of the brain and its structures. Therefore, the MRI-volumetric study of schizophrenia is based on the notion that the structural volume is in some way related to the tissue integrity, which in turn is related in some regular way to its information processing capacity. By this token, the volume of the brain and its structural components will relate to the individual's cognitive ability. Atypical (novel) antipsychotic drugs are known to produce improvement in cognitive functioning in schizophrenia (Meltzer and McGurk, 1999). However, it is presently unclear whether the 'baseline' brain volume and the volume of its structural components are related to the responsitivity to antipsychotic treatment in terms of cognitive improvement.

The present investigation poses the questions: "How is the volume disturbed in schizophrenia?"; "What is the relationship of volumetric alterations to cognitive deficits in schizophrenia?"; and "Does the extent of volumetric alteration relate to the response to the treatment with atypical antipsychotics in terms of cognitive improvement?" .

PART I

CHAPTER 1. SCHIZOPHRENIA: GENERAL INTRODUCTION

The aim of this chapter is to provide a general introduction to the concept of schizophrenia: its origin; its evolution; a debate that the concept provoked since its first formulation; operational criteria for schizophrenia diagnosis and other classificatory approaches; epidemiology; and aetiology of the disorder. The objective is to acknowledge, but not to discuss in depth, the main issues surrounding the concept of schizophrenia, as well as to introduce the terms and definitions that are used throughout the thesis.

1.1. The origin of the concept

Before the 19th century, there was little differentiation between the kinds of insanity. German psychiatrist Emil Kraepelin (1856-1926) advanced the first classificatory system for severe psychological disorders. One of the disorders he described in his *Psychiatrie* in 1896 was *dementia praecox,* borrowing the term from Morel (*dementia precoce* – dementia of early life*)* (Colp, 1995). Kraepelin used the term to refer to different processes that were unified by the fact that they all involved disturbances in thought and behaviour, but in different ways. Thus, he described four sub-types:

i) *simple*, marked by slow social decline, social withdrawal and apathy;
ii) *paranoid*, distinguished by persecutory delusions and fear;
iii) *hebephrenic*, characterised by emotional disturbances inappropriate to context;
iv) *catatonic*, notable by the increased muscle tone, preservation of posture and expression.

In fact, these four types of mental and behavioural disturbances were described as different 'disorders' by other psychiatrists before Kraepelin. Falvet in 1851

described *Folie circulaire* or cyclic madness, corresponding to simple sub-type of Kraepelin. Hecker in 1871 coined the term *Hebephrenia* or a silly, undisciplined mind after Hebe, goddess of youth and frivolity. Kalbaum in 1874 described *Catatonia* and *Paranoia*. Thus, Kraepelin, whether auspiciously or misfortunately, pulled these various concepts under the single disease entity. By doing so Kraepelin, inadvertently, initiated a debate, which continued through the 1st century of schizophrenia and into this century, regarding the core symptoms of the disorder, its boundaries, its different subtypes and their aetiologies, its course and outcome, and so on.

As reflected by the chosen term, Kraepelin defined dementia praecox as characterised by a sudden onset of symptoms early in adulthood and followed by a progressive deterioration, or dementia. In addition to a sudden symptom onset, Kraepelin held that there was "... a group of patients in whom already from childhood upwards a considerable degree of psychic weakness existed" (cited in O'Connell et al., 1997). The core features of dementia praecox in Kraepelin's definition included i) affective disturbances, such as emotional responses that are inappropriate to the context; ii) avolition; iii) anhedonia; iv) stereotyped motor behaviour; v) attentional impairment, vi) sensory experiences in the absence of appropriate stimuli, i.e. *hallucinations*; and vii) beliefs sustained in spite of overwhelming contrary evidence, i.e. *delusions*. As reflected by sub-typing, these symptoms are not present in all individuals with the 'disease'.

Swiss psychiatrist Eugene Bleuler in 1908 disputed the term 'dementia praecox' on the grounds that progressive deterioration of function was not present in all cases, and the complete or partial recovery was evident in at least a third of the individuals. He coined an alternative term *Schizophrenia,* derived from Greek *'schizo'* for split and *'phreno'* for mind. Bleuler's choice of the term reflects his conceptualisation on the nature of schizophrenia as a splitting of thought and emotion, leading to the loosening of the associations. This, in turn, results in disintegration of the normal experience of reality, both external and internal. Bleuler identified four fundamental symptoms of schizophrenia, four 'A's:

i) blunted *Affect* (diminished emotional response to stimuli);
ii) loosening of *Associations* (disturbed patterns of cognition);
iii) *Ambivalence* (inability to make decisions, presumably due to a deficit in the integration and processing of information relevant to the context);
iv) *Autism* (withdrawal into oneself).

Bleuler regarded hallucinations and delusions as 'accessory' symptoms, resulting from the more fundamental disintegration of higher cognitive faculties (Andreasen, 1997).

Overall, Kraepelin and Bleuler agreed on the set of symptoms that define schizophrenia. However, unlike Kraepelin, Bleuler did not hold early onset and progressive deterioration to be the only course of the disorder. He recognised that the disorder was chronic in some cases, but he also asserted that the recovery was possible. Despite these differences, both Kraepelin and Bleuler believed that schizophrenia was a brain disease. These two pioneering scientists initiated the search for a biological basis of schizophrenia.

At around the same time, Adolf Meyer (1866-1950), a brain pathologist, took a completely different approach to understanding the origins of schizophrenia. In Meyer's view, there were no fundamental differences between individuals with schizophrenia and normal people in either biological or psychological make up. Instead, he maintained that schizophrenia was a product of abnormal early learning, leading to the acquisition of maladaptive habits or "adjustive insufficiency".

Thus, even at the genesis of schizophrenia as a clinical entity, two opposing (or complementary) approaches co-existed in clinical practice and scientific research. While Bleuler and Kraepelin founded a biological tradition in schizophrenia research, Meyer gave an impetus to a tradition that focuses on learning and social processes as being central to understanding cognitive and behavioural disorganisation associated with schizophrenia.

Although the subject of the present investigation is conceptually embedded within the biomedical tradition of schizophrenia research, the author acknowledges the importance of environmental and societal factors in shaping schizophrenia phenotype.

1.2. Controversy surrounding the concept of schizophrenia

There has not been a moment in the history of schizophrenia when its nature and even its existence have not been disputed. Some of the issues that have been debated in the course of the 20th century include:

i) Does schizophrenia exist?
ii) Is schizophrenia separate from or coexistent with affective psychosis?
iii) Is schizophrenia a 'disease entity' as originally conceived by Kraepelin and Bleuler?
iv) What are the boundaries of schizophrenia?

i) The first issue is primarily of philosophical and ethical character, as it mainly questions the value of schizophrenia diagnosis and the meaning of the words 'normality' and 'disease', rather than the existence of the schizophrenic phenomena *per se*. Proponents of this movement, which have risen in the 1960s and 1970s, posited important ethical questions and expressed general dissatisfaction towards the orthodox psychiatry of those times in its ability to explain and treat severe psychiatric conditions (Scheff, 1966; Szasz, 1976; Laing, 1967; Laing and Esterson, 1970). Although clinical and scientific validity and utility of schizophrenia concept have not been permanently 'shaken' by the movement, it nevertheless made subtle, but important contributions towards the gradual change in the attitudes with which individuals diagnosed with schizophrenia are treated in clinical practice and in the society at large. The questioning of the value of schizophrenia as a clinical diagnosis in terms of its practical and clinical utility has been recently reopened in the work of van Os (2003).

ii) The second issue goes back to Kraepelin. In his early writings, Kraepelin (1896) has distinguished between schizophrenia and affective disorders that he grouped together as manic-depressive psychosis. The distinction was made on the basis of the course and outcome of the symptoms, with dementia praecox leading to a progressive deterioration following the onset of the symptoms, while affective psychosis leading to a partial or full recovery. However, Kraepelin eventually came to the view that dementia praecox and affective psychosis could coexist and thus a possibility of unitary psychosis cannot be ruled out (Kraepelin, 1920). Bleuler, although separating manic-depressive psychosis, maintained that affective symptoms might coexist with schizophrenia.

The mainstream clinical practice adopted Kraepelin's initial dichotomy between schizophrenia and affective psychosis for the majority of the 20th century. However, the dichotomy has been subjected to a considerable debate and empirical scrutiny. Different multivariate statistical techniques have been employed in order to resolve the question of whether schizophrenia and bipolar disorder may be validly demarcated on the basis of the symptoms assigned to each condition. Most recent factor analytic studies of individual symptoms that included first episode psychotic patients of various diagnoses (i.e. not just schizophrenia and manic depression) have isolated schizophrenia, mania and depression as separate factors despite varying in the overall number of factors (from 4 to 10) that provided the best solution (Kitamura et al., 1995; McGorry et al., 1998; van Os et al., 1999; Rosenman et al., 2000; Cuesta and Peralta, 2001; McIntosh et al., 2001; Serretti et al., 2001). However, the studies also found a considerable overlap in the symptoms associated with different factors. The results of cluster analytic studies are less compelling (International Pilot Study of Schizophrenia, WHO, 1973; Lorr et al., 1966; Everitt et al., 1971) with schizophrenia diagnosis being found across the identified clusters. Kendler and colleagues (1998) used latent class analysis, a type of cluster analysis, in a study of epidemiologically based sample and have found that six-class solution provided the best fit. Although schizophrenia and major depression were easily identifiable as two separate classes, remaining four classes contained patients presenting with a mixture of schizophrenic and affective symptoms. However, cluster analysis assumes mutual exclusivity of the clusters, which does not make it an ideal technique when dealing with 'fuzzy sets' such as psychiatric diagnoses. Perhaps the most compelling argument in favour of the distinction between schizophrenia and manic-depressive psychosis comes from the study that have employed discriminant function analysis, a statistical technique ideally suited to deal with the nature of psychiatric data. Thus, discriminant function analysis carried out as part of the IPSS (WHO, 1979) revealed unequivocal bimodal distribution when schizophrenia was examined separately versus mania and versus depression. Kendell and Gourlay (1970) failed to find bimodal distribution in the initial study of 292 patients diagnosed with schizophrenia and affective disorders, but the results changed to a clear dichotomy in the follow-up study of 128 of these patients when outcome information was taken into account (Brockington et al., 1979).

Another line of inquiry to address this debate is the examination of genetic risk of schizophrenia and affective disorders. Early genetic studies suggested that there is no clear segregation between families that carry schizophrenic or affective genotype. Thus, Rudin (1916) reported that although the risk for schizophrenia for

an individual was high (6.2%) if they had a close relative with schizophrenia, it was higher if the ill relative had a non-schizophrenic (mostly affective) psychosis (8.2%). He also found almost equal numbers of relatives with affective disorder and relatives with schizophrenia in the families of his schizophrenic probands. On the other hand, among the psychotic relatives of Odegaard's (1972) manic-depressive probands, 19% were diagnosed as schizophrenic, indicating that the co-occurrence may run in both directions.

Finally, Adler and Strakowski (2003) have recently evaluated the evidence for and against treating schizophrenia and manic-depressive disorders as separate syndromes. They concluded that whereas schizophrenia and bipolar disorder might be indistinguishable on the levels of phenomenology, cognitive disturbances, and aetiology, there are clear distinctions between two illnesses on the levels of epidemiology and pathophysiology.

Overall, empirical evidence seems to suggest that although schizophrenia and affective disorders might exist in 'clear' forms in some individuals, a considerable proportion of patients exhibit mixed schizoaffective symptoms. Furthermore, as noted first by Kraepelin and as the current data suggests, schizophrenia and affective disorders are best demarcated in terms of long-term outcome, as they can be almost symptomatically indistinguishable at first presentation. Thus, it seems that Kraepelin's distinction stands up when the outcome and overall functional disability of the patients is taken into account. Bleuler's argument is also valid as the studies found, time after time, a substantial proportion of patients presenting with both schizophrenic and affective symptomatology. This has led to the definition and inclusion of *Schizoaffective* disorder into clinical diagnostic manuals to account for the condition, which manifests a mixture of schizophrenia-like and mood disturbances. Research into schizoaffective disorder suggests that patients falling into this diagnostic category tend to have much more favourable outcome and less functional disability then patients with schizophrenia (e.g. Benabarre et al., 2001). The fact that Bleuler had included individuals presenting with the mixture of psychotic and affective symptoms into his definition of schizophrenia might explain why he held that poor outcome and progressive deterioration are not a necessary feature of the disorder.

iii) The third issue is an extension of the first and second debates. The question at hand is whether schizophrenia (or any other psychiatric diagnosis for that matter) has validity as a categorical disease entity or whether psychosis is better understood as a continuum with normality, where 'normal' and

'psychopathological' manifestations represent quantitative variations along this continuum. Similarly, different 'pathological' manifestations (e.g. sub-types) might represent different degrees of illness severity, or alternatively, progressive stages in the longitudinal course of the same illness (Goldberg and Weinberger, 1995).

Bleuler held a continuum position, writing on latent schizophrenia: personality deviation, developing slowly over time, but never reaching a picture of full-blown schizophrenia (Bleuler, 1911). Rado (1953) coined a term 'schizotypy' to refer to a schizophrenia phenotype, characterised by anhedonia, perceptual deviations (particularly perceptual distortions of bodily schema), motivational deficit, and inability to organise goal-directed activities, presumably casued by a genetic predisposition. Meehl (1962, 1990) conceptualised schizotypy in a similar way, highlighting innate neural or biochemical defect (schizotaxia) as the basis for schizotypal personality, which in some cases may lead to the complete picture of schizophrenia as a consequence of maladaptive learning and under the influence of environmental factors. Menninger and colleagues (1958) re-introduced the concept of a 'unitary psychosis', which existed prior to Kraepelin's categorisation of mental illnesses. The above mentioned approaches to the continuum between schizotypy and schizophrenia have been characterised as quasi-dimensional (Claridge, 1985; Claridge and Beech, 1995), since they focuse on the variations within the illness domain, taking the 'ill' state as a reference point and constuing dimensionality as degrees of expression of a disease process. Claridge (1985, 1987) advanced a 'fully' dimensional position, holding that schizotypal behavioural and psychological traits fall within the normal, broadly healthy, domain. Crow (1990) proposed that schizophrenia genotype is linked to the emergence of language in human species, and hence is normally distributed within the population, varying from benign to moderate, and to malignant.

iv) The debate as to what is and what is not schizophrenia has been also fuelled by the fact that the symptoms defining schizophrenia are not pathognomonic, i.e. observed in other conditions. Thus, psychomotor symptoms such as akinetic mutism, catatonia and abulia that are present in some individuals with schizophrenia, also occur in a wide range of psychiatric conditions, including dementia, the autistic spectrum disorders, as well as in patients with brain lesions. Psychotic symptoms, such as hallucinations and delusions can also be observed in other psychiatric and neurological conditions, including post-traumatic stress disorder, obsessive-compulsive disorder, dementia, velo-cardio-facial syndrome (VCFS), temporal lobe epilepsy and others. Prescription medication as well as drugs of abuse can also induce symptoms characteristic of schizophrenia. The solution to

this problem in contemporary clinical practice is to rule out these alternatives before assigning schizophrenia diagnosis, i.e. a differential diagnosis.

1.3. Diagnosis and classification of schizophrenia

1.3.1. The operational criteria for schizophrenia diagnosis

Due to the factors discussed in the preceding section, the definition of schizophrenia evolved over time. The most recent diagnostic tool that is most widely applied in clinical as well as in research settings is the Diagnostic and Statistical Manual, forth version (DSM – IV), which was offered in 1994 by the American Psychiatric Association (APA) (see *Table 1.1*). It is important to note that DSM-IV criteria does neither imply nor intend to state that schizophrenia has empirical validity as a disease entity. The intention of the DSM-IV is to provide a tool for a reliable diagnosis for the purposes of treatment and scientific research.

TABLE 1.1. DSM-IV criteria for schizophrenia diagnosis

Diagnostic criteria
A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less, if successfully treated): 1) Delusions 2) Hallucinations 3) Disorganised speech 4) Grossly disorganised or catatonic behaviour 5) Negative symptoms, i.e. affective flattening, alogia, or avolition
B. *Social/occupation dysfunction*
C. *Duration*: Continuous sings of the disturbances for at least 6 months, which may include the prodromal or residual periods
D. *Schizoaffective and mood disorder exclusion*
E. *Substance/general medical condition exclusion*
F. *Relationship to a pervasive developmental disorders*: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less, if successfully treated).

The DSM-IV diagnosis of schizophrenia includes substantive and temporal criteria. The *substantive* criteria include gross impairment of reality testing, involving incorrect inferences about reality and inaccurate evaluation of one's own thought process, i.e. *psychosis*. Psychosis implies substantial departure from the range of normal tendency to under- or over-value one's abilities and to maintain one's belief in the face of contradictory evidence. The disturbances must affect at least two of several psychological processes, including thought, perception, emotion, communication, and psychomotor behaviour. The *temporal* criteria are the duration of symptoms for at least six months, leading to marked deterioration from the individual's previous levels of social, vocational and self-care functioning induced by those symptoms.

The disturbances of thought processes are called *delusions*, while perceptual disturbances are called *hallucinations*. Delusions are false beliefs that resist all argument and are sustained in the face of evidence that normally would be sufficient to destroy them. Hallucinations are sensory experiences with the compelling sense of reality in the absence of external stimulation of the corresponding sensory modality. Auditory hallucinations are most prevalent, but visual, tactile or olfactory hallucinations also occur.

To reflect the fact that the symptoms of schizophrenia overlap with other psychiatric conditions, DSM-IV includes a number of exclusion criteria that have to be made in order to rule out other causes for the observed symptoms.

1.3.2. DSM-IV sub-types

There are four sub-types of schizophrenia according to DSM-IV criteria: *paranoid*, *disorganised*, *catatonic* and *residual*. *Paranoid* sub-type is characterised by delusions of persecution and/or grandeur, typically auditory hallucinations and by either intensely emotional or very formal behaviour during social interaction. *Disorganised* sub-type is characterised by body-centred delusions and/or hallucinations and, most markedly, idiosyncratic and incoherent behaviour, such as grimaces, giggles or bursts of laughter without an apparent stimulus. *Catatonic* sub-type is distinguished by delusions centred on death and destruction as well as very excited or, on the contrary, 'frozen' behaviour. *Residual* sub-type typically does not involve delusional or hallucinatory content, but characterised by 'flat' or blunted affect, and in some cases impairment of hygiene and/or peculiar behaviour.

In the present thesis, the term *'schizophrenia'* is taken to refer to a broad range of phenomena covered by the DSM-IV operational criteria for schizophrenia diagnosis. The expression *'schizophrenia patient'* (or *'patient with schizophrenia'*) is employed to refer to anyone with a diagnosis of schizophrenia according to DSM-IV operational criteria or other accepted diagnostic methods, such as International Classification of Diseases, 9th or 10th revision (ICD 9, ICD 10).

1.3.3. Other classifications of schizophrenia

In addition to the criteria and sub-types of schizophrenia offered in DSM-IV, other ways of classifying schizophrenia have been proposed. One of the approaches was to characterise schizophrenia according to the onset and progression of the symptoms. *Acute* vs. *chronic* distinction has been made (Andreasen and Carpenter, 1993). *Acute* schizophrenia is characterised by a rapid and sudden onset of florid symptoms. Frequently, the onset would be precipitated by a specific factor, such as a stressful life event (Arieti, 1974) or high expressed emotion in the family (Bebbington et al., 1993; Butzlaff and Hooley, 1998), in which case a 'reactive' type of schizophrenia would develop. In contrast, *chronic* sub-type would manifest as a gradual and prolonged history of withdrawal, with no apparent triggers, in which case 'process' schizophrenia would be present. In clinical practice, the acute-chronic distinction is made on the basis of the number of episodes a person has had and the length of hospitalisation. The first episode that results in hospitalisation for less than a year or several episodes with very brief hospitalisations leads to an acute classification. Hospitalisation for two years and over results in chronic classification. However, these criteria have low reliability of classification as it becomes difficult to distinguish between acute and chronic presentations in persons who require more than a year but less than two years of hospitalisation.

Another approach is based on aetiology, namely familial aggregation. Patients with familial history of schizophrenia are assumed to have a genetic basis, whereas patients without such history are thought to be affected by environmental factors. The review of the research into familial vs. non-familial cases of schizophrenia, with familial assumed to represent more severe form of the disorder with poorer prognosis, have concluded that there are no ascertainable differences in symptomatology, age of onset, premorbid functioning, outcome and treatment response (Roy and DeVriendt, 1994).

Other approaches to classifying schizophrenia capitalised on heterogeneity in terms of the outcome and treatment response. A proportion of people with schizophrenia responds well to antipsychotic medication, i.e. '*responders'*, and are able to maintain work and social interaction, whereas approximately one quarter to one third of patients remain treatment refractory with classic neuroleptics, i.e. '*non-responders*', and are often socially isolated and service dependent (Vaillant, 1964; Stephens et al., 1966). However, this picture is changing with the advent of novel atypical antipsychotics (Smith et al., 1996; Campbell et al., 1999).

Crow (1980) has proposed a classification that combines different forms of heterogeneity in schizophrenia to derive two sub-types, *Type I* and *Type II*. He combined such variables as the symptom type or cluster, response to antipsychotic medication, cognitive functioning and pathophysiological markers. Thus, *Type I* schizophrenia is acute; characterised by *positive symptoms,* such as delusions, hallucinations and positive thought disorder; treatment responsive; cognitively intact; and involves dopamine dysfunction. *Type II* schizophrenia is chronic; characterised by *negative symptoms,* such as flat affect, poverty of speech, and loss of volition; treatment refractory; cognitively impaired; and involves structural brain abnormalities such as an enlargement of lateral and third ventricles.

Crow's typology brought the positive-negative symptoms dichotomy into the forefront of schizophrenia research. It was supported by other investigators (e.g. Andreasen and Olsen, 1982). However, whereas Crow's model (1980) implied the existence of distinct sub-types of categories, Andreasen (1985) argued that these symptom clusters are better viewed as dimensions, which are continuous and additive, and has shown that most patients have a considerable overlap of positive and negative symptoms.

Liddle (1987a) has extended the positive/negative duo of symptom clusters by adding a third syndrome of psychomotor poverty. This tertiary syndrome structure of symptoms characteristic of schizophrenia has since been supported by a number of investigators (e.g. Arndt et al., 1991; Brown and White, 1992). Each syndrome was found to be associated with a specific pattern of neuropsychological and pathophysiological alterations (Liddle, 1987b): i) *psychomotor poverty* being associated with deficits in abstract thinking, long-term memory and left-sided prefrontal hypofunction; ii) *disorganisation* (negative syndrome) with deficits in concentration, short-term memory, learning and decreased perfusion in the right ventral prefrontal cortex and insula, and increased perfusion in the right anterior

cingulate; iii) *reality distortion* (positive syndrome) with poor figure-ground perception and left medial temporal lobe hyperfunction and left lateral temporal lobe hypofunction.

1.3.4. One disease or many?

The heterogeneous clinical presentation of schizophrenia led some to argue that in order to establish its aetiology and pathophysiology, it should not be treated as one disorder. Instead, homogeneous sub-types should be established, the aetiology and pathophysiology of which can than be traced. All different ways of classifying schizophrenia reviewed in the preceding section have been initially advanced as the potential sub-types of schizophrenia, along with sub-types delineated in DSM-IV. However, none has proved to be fully reliable. Goldberg and Weinberger (1995) have presented a case against sub-typing in schizophrenia, arguing that: (i) subtypes have only modest stability, with patients manifesting distinct classes of symptoms at different stages of illness; (ii) different syndromes co-occur in the same patient at the same time point; (iii) studies showing differences between presumed sub-types in pathophysiology, neuroanatomy, or neurocognition can be interpreted as showing different degrees of illness severity. They thus concluded that a simple model of schizophrenia in which patients vary along severity dimension should be favoured for the sake of parsimony. For the purposes of the present investigation, this simple dimensional approach to schizophrenia is adapted.

1.4. Epidemiology

1.4.1. Prevalence

Prevalence is defined as the number of cases (per 1000 persons at risk) in a population at any given time (point prevalence) or over a defined period of time (period prevalence). Prevalence rates for schizophrenia found in the studies with the least methodological problems vary depending on the diagnosis used, as well as the population studied, and range from 1.4 to 4.6 cases per 1000 population (review, Jablensky, 1995).

1.4.2. Incidence

The incidence rate is defined as annual number of new cases in a defined population per 1000 individuals at risk, and is more representative of the morbidity (i.e., the probability of disease occurrence at a point in time) than the prevalence rates. The World Health Organisation (WHO) 10-country investigation (Sartorius et al., 1986; Jablensky et al., 1992) has found a rate of between 0.16 and 0.35 per 1000 cases when ICD-9 criteria for schizophrenia was used, which includes broader range of cases, and the rate of between 0.07 and 0.14 when a 'narrow' diagnosis of schizophrenia was used (as defined by the Schneiderian first-rank symptoms: auditory hallucinations, delusions, thought broadcasting/insertion/withdrawal, and passivity phenomena).

1.4.3. Morbid risk (disease expectancy)

The probability of a single individual developing a disease if he/she survives through the entire period of risk for that disease defines the morbid risk. As most studies have produced morbid risk estimates in the range of 0.50-1.60% (Jablensky, 1995), the often quoted morbid risk of schizophrenia is about 1%.

1.4.4. Spatial distribution

There are comparable rates of schizophrenia in developing countries and industrialised societies (Torrey, 1980). However, there might be a greater prevalence of schizophrenia amongst the poor inhabitants of the large urban areas. Some American studies have found the rate of schizophrenia being eight times as high in the lower classes than it is in the middle or upper social classes (e.g. Saugstad, 1989). This phenomenon is known as 'downright shift' hypothesis of schizophrenia, which postulates that persons who become schizophrenic drift down a social class from that of their parents through a process of *social selection*. In addition, the prevalence of schizophrenia might be higher amongst immigrants, as has been found in a few studies from different countries (e.g. Haasen et al., 2001; McGrath et al., 2001; Cantor-Graae et al., 2003). This later finding indicates that *social causation*, perhaps due to social isolation and stress associated with adapting to a new culture, has a role in schizophrenia aetiology.

1.4.5. Antecedents, course and outcome

At least some individuals who later in life receive a diagnosis of schizophrenia differ from their peers from very early in life. Delays in reaching developmental milestones, neuromotor and visuo-motor anomalies, cognitive deficits, and prolonged impairment in social functioning are apparent throughout the premorbid history of schizophrenia patients (Jones and Tarrant, 2000). About three quarters of individuals experiencing the first psychotic episode show a prodromal phase of about five years. In 68 % of the cases the pre-phase (the time between the first positive symptom and the climax of positive symptoms) exceeds one year, in 15% of the cases the onset is sub-acute (the pre-phase of four weeks to one year), and in 18 % of the cases the onset is acute (the pre-phase of under four weeks) (Hafner & Nowotny, 1995).

About 40% of individuals presenting first psychotic episode will have a chronic course of the disorder with persistent or re-current symptomatic episodes accompanied by profound and lasting social and occupational dysfunction. Approximately 25% of individuals will experience only one episode with total recovery, while about 35% will have several episodes with subsequent remission and minimal social impairment. In most cases, the course appears to be established within the first five years following the onset (Frangou & Murray, 1996).

Factors that are predictive of outcome include premorbid adjustment (Bailer et al., 1997), the type of onset (Jablensky et al., 1992), marital status (Childers and Harding, 1990), supportive social relationship (Nuechterlein et al., 1992), symptom typology (Andreasen et al., 1990) and cognitive function (Green, 1996). Thus persons with an insidious onset, who show poor premorbid adjustment, the absence of extended social network, manifest predominantly negative symptoms and have poor cognitive abilities will have the worst prognosis clinically and functionally.

There might be gender differences in terms of the premorbid history, age of onset, lifetime risk, and prognosis. Women generally show better premobrid adjustment, a higher percentage of remitting illness episodes and shorter hospital stays, higher survival rate, and better functional outcome (WHO, 1979; Childers and Harding, 1990; Jablensky et al., 1992). There are well-established differences in the mean age of onset between two sexes. WHO 10-country study has found the mean age of onset for men at 25.3 years and for women at 28.9 years (Hambrecht and

Hafner, 1992). Furthermore, men and women show different age-incidence curves. For men, the risk of developing schizophrenia picks between the ages of 20-24 years with the subsequent low and stable incidence rate, whereas women show much lower risk at this age range, with the sharply increasing incidence in age groups older than 35. However, the life-time risk for developing schizophrenia might be higher in women (Bojholm and Stromgren 1989; Helgason and Magnusson, 1989), when the cases with the late-onset schizophrenia and late paraphrenia (late-onset paranoid psychosis) are included. A protective, neuroleptic-like effect of oestrogen on central dopaminergic neurotransmission (Seeman and Lang, 1990), an earlier maturation of the central nervous system in women (Saugstad, 1989) and genetic factors (DeLisi, 1992) have been proposed to account for these gender differences in the age of onset and incidence curves.

1.5. Aetiology

In this section, the genetic, neurochemical, and functional neural dysfunction causes of schizophrenia will be overviewed. The pathophysiological account, namely structural brain alterations, will be reviewed in detail in the following chapter (Chapter 2).

1.5.1. Genetics

The role of genetic factors is well established in schizophrenia. The study of monozygotic twins suggests that genetic contribution to schizophrenia aetiology is about 42% (Shields and Gottesman, 1972). The concordance rates of schizophrenia for dyzogotic twins is about 9%, suggesting that it is unlikely that the same uterine environment is the reason for the 42% association in identical twins. Adoption studies also provide support for unambiguous, albeit moderate, genetic influence. Heston (1966) found that adopted children of schizophrenic mothers were five times more likely to be diagnosed with schizophrenia than those of normal mothers. Finally, first-degree relatives of schizophrenia probands are 18 times more likely to be diagnosed with a schizophrenia spectrum disorder (Kendler et al., 1985).

Identification of relevant genes is a much more arduous task than simple establishment of a genetic contribution to schizophrenia aetiology. At the present, there are as many candidates to schizophrenia susceptibility genes as there are

sources of schizophrenia heterogeneity. One of the earliest 'suspects' was a cluster of genes on chromosome 5 (Sherrington et al., 1988); however, subsequent studies did not find this cluster to be associated with susceptibility to schizophrenia (Crowe et al., 1991). The most robust evidence to date exists for the genes encoding D-3 dopamine and 5-HT2a receptors, as well as a deletion of chromosome region 22q11 to be associated with a small rise in susceptibility to schizophrenia (review, McDonald and Murphy, 2003).

One of the promising lines of inquiry into genetics of schizophrenia was opened recently by Weinberger and his collaborators. Their approach is based on taking well-characterised functional and neuropsychological deviances in schizophrenia as a departure point and mapping these known factors to particular genetic polymorphisms via the use of functional magnetic resonance imaging (fMRI). For example, abnormal prefrontal information processing is one of the characteristics of schizophrenia phenotype, and is found in unaffected individuals who are genetically at risk. Weinberger and colleagues (2001) have found that catechol-o-methyl transferase (COMT) genotype, which affects enzyme activity and appears to uniquely impact prefrontal dopaminergic neurotransmission, predicts performance on prefrontal executive and working memory tasks. They have also found, through family-based association studies, that excessive transmission of the COMT valine (val) allele to schizophrenia offspring is related to poorer prefrontal function. Taken together, these findings suggest that the COMT val allele increases risk of schizophrenia by virtue of its effect on dopamine-mediated prefrontal information processing.

Overall, the search for schizophrenia susceptibility genes is taken on many different directions. As there is a growing awareness that both schizophrenia patients and their relatives have cognitive impairments (discussed in *Chapter 2*), the genetic projects attempting to link different genetic polymorphisms with specific cognitive processes might be a valid and fruitful approach to discovering genomes that produce susceptibility to mental illness in general and schizophrenia in particular.

1.5.2. Neurochemistry

Neurochemical imbalances in schizophrenia have been one of the central aetiological factors to be studied since the discovery of antipsychotics in the 1950s and their ameliorating effects on positive symptoms. Almost all known

neurotransmitters of the central nervous system have been implicated since than, including serotonin (Wooley and Shaw, 1954), noradrenaline (Stein, 1971), GABA (Roberts, 1972), and glutamate (Kim et al., 1980), with the dopamine hypothesis giving the first impetus to and dominating the neurochemical studies of schizophrenia.

According to the dopamine theory in its simplest form, schizophrenia, or more precisely its psychotic symptoms, is the result of sub-cortical dopaminergic hyperfunction (e.g. Carlsson et al., 1988). Dopaminergic neurotransmission mediates the rewards mechanisms in the brain, and seems to modulate the salience of the stimuli, either external or internal. The increased, to the point of overwhelming, salience of the stimulus, which would be considered trivial in the 'normal' state of mind, is central to the phenomenal quality of a psychotic state (Hemsley, 1994; 1998). A few models of psychosis pathogenesis have been advanced, all of them featuring the effects of increased dopamine activity in ventral striatum and its effect on the function of cortico-striato-pallido-thalamic circuitry (Buchsbaum, 1990; Carlsson and Carlsson, 1990; Grace, 1991; Gray, 1995; 1998; Csernansky and Bardgett, 1998; O'Donnell and Grace, 1998).

The dopamine hypothesis emerged from four related tenets. First, the common denominator of the first generation of antipsychotic drugs is the blockade of D2 receptors (Carlsson and Lindqvist, 1963). Second, the side effects of conventional antipsychotic drugs are similar to the symptoms of Parkinson's disease, a condition associated with low levels of dopamine, which is improved through the use of L-dopa. Third, the agents that are dopamine receptor agonists, such as amphetamine, can induce psychotic states similar to those observed in schizophrenia (Angrist et al., 1974). Forth, dopamine agonists aggravate the symptoms in schizophrenia patients (Meltzer and Stahl, 1976).

However, there are some important caveats to the DA hypothesis as based on this evidence. First, these pharmacologically based facts implicate dopamine only indirectly. One of the predictions based on this evidence is that people with schizophrenia would have an increased density of DA2 receptors. The systematic positron emission tomography (PET) studies of DA receptor densities in drug-naïve schizophrenia patients did not observe the density increase (review, Nordstrom et al., 1993). However, in more recent years it has been demonstrated that drug-naïve schizophrenia patients show increased synthesis (e.g. Hietala et al., 1994) and elevated release of dopamine (e.g. Laruelle et al., 1996), and that the elevated release correlates with the induction of positive symptoms (e.g. Breier et al.,

1997). Second, only about a third of the patients respond to treatment with antidopaminergic drugs, with patients having predominantly negative symptoms showing a poor response, despite having high levels of D_2 blockade (Pilowsky et al., 1993). Third, dopamine-agonist induced psychosis can only mimic one sub-type of schizophrenia, namely paranoid, and even with this limitation, there are differences between, for example, amphetamine induced psychosis and paranoid schizophrenia, such that amphetamine psychosis is not accompanied by affective blunting and the formal thought disorder. Non-paranoid forms of schizophrenia, with predominantly negative symptomatology, are best mimicked by phencyclidine (PCP, Luby et al., 1962), which predominantly acts antagonistically on the glutamatergic N-methyl-D-asparate (NMDA) receptors (Lodge and Anis, 1982). Finally and importantly, it takes several weeks for antipsychotic treatment to alleviate schizophrenic symptoms whereas the effects of the drugs on neurotransmitter systems occur within hours.

Therefore, it has been suggested (Laruelle et al., 1996) that abnormalities could reside in the control of dopamine function rather than dopaminergic neurotransmission *per se*. Subsequently, greater emphasis was put into understanding the systems modulating or acting on dopamine neurons and their mutual interactions, cortically and sub-cortically (e.g. Carlsson and Carlsson, 1990: glutamatergic and monoaminergic interactions; Joyce, 1993: dopaminergic, serotonergic and noradrenergic limbic interactions; Yamamoto et al., 1994: noradrenergic and dopaminergic interactions; Carlsson, 1995, Carlsson et al., 1997: dopaminergic, glutamatergic, GABAminergic, noradrenergic, serotonergic and acetylcholine systems). With the introduction of the atypical antipsychotics, which have a close affinity for several receptors besides the D2 dopaminergic, including D1, D3, D4, 5-HT2, and NMDA, making them efficacious in reducing not only positive but also negative and cognitive symptoms, it became clear that many other receptor sites apart from D2 are likely to be involved in the pathogenesis of schizophrenia (Seeman, 1992; Kerwin and Taylor, 1996). (A more detailed discussion of atypical antipsychotics and the mechanisms of their efficacy is presented in *Chapter 3*).

To conclude, dopamine hypothesis rests on fairly strong pharmacological and psychopathological evidence. The antagonism of D2 receptors still remains a prerequisite for a drug to have an ameliorating effect on psychotic symptoms. However, it is unlikely that the dysfunction of dopaminergic system alone can account for the wide spectrum of symptoms and cognitive dysfunction characteristic of schizophrenia. Moreover, since a primary disturbance in one

neurotransmitter function will inevitably influence other systems, it seems unreasonable to expect that the neurochemical aetiology of schizophrenia can be deduced with confidence. Finally, different sub-types of schizophrenia might have different primary neurochemical aetiologies.

1.5.3. Functional brain abnormalities

A disturbance of functional neural circuitry, possibly as a result of morphological and neurochemical alterations, was proposed to play a causal role in schizophrenia (e.g. Andreasen et al., 1998; Friston et al., 1999). The first reports of abnormal brain function as demonstrated by brain imaging techniques were of 'hypofrontality' in schizophrenia patients at rest, as measured by the regional cerebral blood flow (Ingvar and Franzen, 1974). However, in studies of patients at rest, 'hypofrontality' has been an inconsistent finding, since resting is physiologically and psychologically variable event (review, Weinberger and Berman, 1996).

Hypofrontality has been linked with executive dysfunction in schizophrenia. Weinberger et al. (1986) demonstrated attenuated activation of the dorsolateral prefrontal cortex during performance on the Wisconsin Card Sorting test (WCST) in unmedicated patients. More recently, Riehemann et al. (2001) have replicated this finding. In subsequent studies, Weinberger and colleagues demonstrated that the DLPFC hypoactivation during WCST was correlated with reduced dopaminergic activity (Weinberger et al., 1988) and reduced hippocampal volume (Weinberger et al., 1992). These findings suggest that structural and neurochemical alterations underlie disrupted brain function in schizophrenia.

Cognitive activation paradigms have shown prefrontal hypofunction in schizophrenia patients during working memory (e.g. Perlstein et al., 2003), sustained attention (e.g. Barch et al., 2001), selective attention (inhibition of preportent response) (Rubia et al., 2001), but these results have been challenged as artefacts of poor performance. Furthermore, some studies failed to find hypofrontatlity during cognitive task performance (e.g. Honey et al., 2002), and some even observed hyperfrontality (e.g. Callicott et al., 2000; Manoach et al., 2001; Ramsey et al., 2002).

Interestingly, fMRI studies demonstrated altered patterns of activations in patients on the tasks of higher cognitive functions in which their performance was on the level of normal controls. Thus, Ramsey et al. (1999) found reduced activation of

the left frontal cortex in the absence of set-shifting deficit. Similarly, Goodman et al. (1999) observed abnormal brain activation during normal performance level on a working memory task. Mitchell and colleagues (2001), reviewing the findings of fMRI studies in schizophrenia, suggested that schizophrenia might be associated with functional reorganisation during brain development.

Abnormal co-activation between different brain regions has been also observed in schizophrenia during higher cognitive processing. Yurgelun-Todd and colleagues (1996) observed lower activation of frontal but increased activation of temporal cortex during word production in schizophrenia patients relative to normal controls. Volz and colleagues (1997) observed a lack of prefrontal activation and a trend towards increased *left* temporal activation during WCST performance in patients relative to normal controls. In addition, Liddle and colleagues (1999) found that patients failed to suppress left temporal response during working memory task, and proposed abnormal coordination of activity between frontal and left temporal cortices underlying higher cognitive (dys)functioning in schizophrenia.

Abnormal neuronal activity in schizophrenia has been also observed on the tasks of basic information processing. Wible and colleagues (2001) reported underactivation of superior temporal gyrus in patients relative to normal controls at the earliest stages of sensory input as measured by an auditory mismatch negativity paradigm (identification of deviant tones from a string of standard tones). Braus et al. (2002) found reduced activation of higher association cortices, including prefrontal and parietal, during simple sensory processing paradigm. Kumari and colleagues (2002a) observed reduced activation of a functional network involved in procedural learning, including the thalamus, the striatum, the precuneus, the cingulate gyrus and the premotor cortex. Reduced thalamic and basal ganglia activation was seen during deficient prepulse inhibition of the startle response, a measure of sensorimotor gating, in schizophrenia (Kumari et al., 2003a). These data point to widespread functional neural dysfunction in schizophrenia affecting sensory and association cortices, as well as subcortical structures.

Functional neuroimaging studies have linked clinical features of schizophrenia to the disordered neural function. Negative symptoms have been linked to prefrontal hypofunction (e.g. Andreasen et al., 1992), auditory hallucinations to the activation of temporal lobe, particularly its anterior pole (e.g. Kurachi et al., 1985), whereas visual hallucinations have been shown to associate with the activation of extrastriate visual cortices (ffytch et al., 1998).

CHAPTER 2. SCHIZOPHRENIA: STRUCTURAL ALTERATIONS, COGNITIVE DEFICITS, AND THEIR INTER-RELATIONSHIPS

In this chapter, structural alterations in schizophrenia will be overviewed, followed by the evaluation of the pattern of the cognitive deficits and their current place in schizophrenia research. These will be followed by a detailed up-to-date review of the literature on the structure/cognition relationship in schizophrenia.

2.1. Introduction

Kraepelin (1919) and Bleuler (1911) were the first to propose that schizophrenia might be a brain disease. They were also the first to observe and to study cognitive dysfunction in the patients they were treating. Both Kraepelin and Bleuler viewed cognitive dysfunction as a core feature of schizophrenia, with hallucinations and delusions being secondary or 'accessory' symptoms. However, despite these early conceptions of schizophrenia aetiology, the study of brain abnormalities, cognitive deficits and their possible inter-relationship took almost a century to establish itself as one of the primary lines of inquiry in schizophrenia research.

Since the seminal Computer Topography (CT) study by Johnstone and colleagues (1976) that reported lateral ventricular enlargement in schizophrenia patients and cognitive deficits associated with the enlargement, there were a number of MRI studies that have studied neuropsychological correlates of structural brain alterations in schizophrenia. However, there has not been a comprehensive review of MRI/neuropsychological studies since the publication by Gur in 1992. The aim of this chapter is to introduce the issues of structural alterations and cognitive deficits in schizophrenia and to review the findings of the magnetic resonance imaging (MRI) studies that have examined their inter-relationships.

2.2. Structural Alterations

2.2.1. Methods of quantifying structural alterations

Two methods currently employed for the study of volumetric brain alterations include a region of interest (ROI) approach, which is historically older and is considered to be the Gold Standard, and the Voxel Based Morphometry (VBM) (Ashburner and Friston, 2000), which was first applied in 1995 by Wright and colleagues to the study of schizophrenia.

The ROI method involves manual outline of the regions of interest on a structural image, pixel by pixel, and is therefore susceptible to inter-rater bias and variations in landmark identification. It is also extremely time consuming, positing limits on the number of brain regions measured, and thus preventing the comprehensive identification of regional alterations in any given sample.

The VBM is an automatic technique, which allows the comparison of grey (or white) matter tissue availability between the groups on the voxel-by-voxel basis through the entirety of the brain and identifies differences of highly spatially localised nature. It therefore overcomes the limitations posited by the ROI technique by being objective and comprehensive. The VMB allows the examination of two tissue availability indices: concentration and volume (Ashburner and Friston, 2000). The concentration within the VBM context is understood as a proportion of a measured tissue type relative to other tissue types within a region (the size of which is determined by the size of the smoothing kernel applied during the image pre-processing, usually 12 mm). The volume is an absolute amount of a measured tissue type within a region in relation to the rest of the brain. (A more detailed account of the VBM method is provided in *Chapter 5, Method*).

2.2.2. The pattern and the nature of structural alterations

2.2.2.1. ROI studies

The volumetric alterations identified with ROI approach are subtle but widespread, including an array of cortical and sub-cortical brain regions (review, Shenton et al., 2001). However, not all of the brain pathological findings are consistently replicable, perhaps due the heterogeneity of schizophrenia illness, its gender dimorphic manifestation, as well as possible non-static presentation of the condition (see Shenton et al., 2001 for more details).

Amongst the most robust findings is the ventricular enlargement. The enlargement of lateral ventricles (LV) in individuals with schizophrenia has been the most replicable finding in the history of psychiatry. It is found in 80 % of the studies that measured this structure (Shenton et al., 2001). The enlargement is present in 20% to 40% of patients with chronic schizophrenia (Shelton and Weinberger, 1986) and seems to be more pronounced on the left side of the brain (Losonczy et al., 1986), especially in the region of the temporal horn (Becker et al., 1990; Shenton et al., 1992). It has been noted in the unaffected siblings and relatives of schizophrenia patients as compared to healthy subjects (Sharma et al., 1998; McDonald et al., 2002). Although some studies have found the LV size to be stable over time, there are reports of progressive enlargement with the duration of the illness, with the rate of change greater on the left (DeLisi et al., 1995, 1997). Enlargement of the third ventricular size has been found in 73% of the studies that measured this structure (Shenton et al., 2001).

The ventricular enlargement has been interpreted as an indirect evidence of the grey matter loss of the structures immediately adjacent to the lateral and/or the third ventricles, including amygdala, hippocampus, and thalamus. Indeed, one of the most replicable findings of MRI studies (74% of 49 studies) is the reduction in the size of the medial temporal lobe structures such as amygdaloid/hippocampal complex in chronic schizophrenia patients relative to healthy controls (Shenton et al., 2001). A reduction of this region is also reliably found in first episode patients (Bogerts et al., 1990; Lawrie et al., 1999; Copolov et al., 2000). The reduction of the thalamus is not found as reliability, 42% of the studies (Shenton et al., 2001), but this might be due to the difficulty in delineating thalamus with the ROI method.

Other grey matter reductions found in schizophrenia include (in the order of replicability): superior temporal gyrus (100% of the studies); whole temporal lobe (61%); frontal lobe (60%); parietal lobe (60%); occipital lobe (44%); cerebellum (31%); and whole brain volume (22%) (Shenton et al., 2001). Grey matter increases are found in the basal ganglia structures (caudate, putamen, and globus pallidus) by 65% of the studies (Shenton et al., 2001), although three studies observed grey matter reduction of the caudate (Mion et al., 1991; DeLisi et al., 1991a; Rossi et al., 1994), which might be associate with tardive dyskenisia (Mion et al., 1991). Abnormalities in white matter volume have also been reported (Cannon et al., 1998; Wolkin et al., 1998), but not as consistently as those for the grey matter (review, Lawrie and Abukmeil, 1998). Lack of normal hemispheric

asymmetry in schizophrenia patients has also been found (Bilder et al., 1994, Sharma et al., 1999).

In terms of the magnitude of the volumetric abnormalities, meta-analysis of 58 studies (published before August 1998) by Wright and colleagues (2000) revealed an absolute cerebral volume reduction of 2%, with greater relative reductions in the volume of grey (2%) rather than white (1%) matter. Ventricular volumes were increased by 26%, with the body of the lateral ventricles being increased by 16% bilaterally and the left temporal horn of the lateral ventricles being increased by 10% relative to the absolute ventricular volume increases. Frontal lobes were reduced by 2% relative to the absolute cerebral volume reduction. A reduction of temporal lobe volume did not exceed overall cerebral volume differences; except for the left anterior superior temporal gyrus with 7% relative reduction. Medial temporal lobe structures showed a substantial volume reduction relative to the global cerebral differences, with amygdala being reduced by 6% bilaterally; amygdaloid/hippocampal complex by 6% on the left and 5% on the right; hippocampus by 2% on the left and 3% on the right; and parahippocampal gyrus by 7% on the left and 5% on the right. Relative volumes of the thalamus were also reduced by 4% for the left and 3% for the right. Basal ganglia volumes were increased relative to the global cerebral volumes: left caudate by 4%, right caudate by 2%, putamen by 6% bilaterally, left globus pallidus by 21%, and right globus pallidus by 24%. Gender differences for volume changes were observed only for total ventricular volume increases with 30% for the male and 16% for the female patients.

2.2.2.2. VBM studies

The studies utilising VBM methodology have recently converged on most of these findings, plus added to the list of local brain tissue alterations in the regions that have not been previously measured by the ROI studies, such as grey matter reductions in the middle temporal gyrus (Job et al., 2002), insula (Wright et al., 1999; Wilke et al., 2001; Kubicki et al., 2002), precentral (Anath et al., 2002; Job et al., 2002) and postcentral gyri (Anath et al., 2002), fusiform gyrus (Anath et al., 2002), uncus (Job et al., 2002), inferior parietal lobule (Anath et al., 2002), peristriate visual cortex (Anath et al., 2002), and right middle occipital gyrus (Ananth et al., 2002), as well as the reductions of the white matter of the right superior occipitofrontal fasciculus (Suzuki et al., 2002), bilateral anterior limbs of the internal capsule (Suzuki et al., 2002), and the lateral optic radiation (Ananth et al., 2002). The increases in local brain tissue have also been reported, including the grey matter of the left insula (Wilke et al., 2001), right putamen (Wilke et al.,

2001), right paracentral lobule (Suzuki et al., 2002), precuneus (Suzuki et al., 2002), bilateral cuneus (Suzuki et al., 2002), superior parietal lobule (Suzuki et al., 2002), bilateral declive and the right culmen of the cerebellum (Wilke et al., 2001).

The VBM studies highlight the widespread pattern of structural alterations through the cortical and sub-cortical areas in any given cohort of schizophrenia patients. Moreover, although some of the findings appear to be replicable, other findings might be specific to the population of patients studied, and might be related to the differences in clinical features, symptomatology, and neurocognitive deficits.

2.2.3. The aetiology of structural alterations: neurodevelopmental, neurodegenerative and 'the three hit' models

At least three competing types of pathophysiological models have been proposed to account for structural brain alterations in schizophrenia. Neurodevelopmental models proposed by Murray and Lewis (1987) and Weinberger (1987) have stemed from the observations of premorbid abnormalities (e.g. Erlenmeyer-Kimling and Cornblatt, 1992), as well as high incidence of pre-natal and birth complications in individuals who later develop schizophrenia (e.g. Jones and Cannon, 1998). Essentially, neurodevelopmental theories maintain that an earlier lesion due to intra-uterine viral infection especially during late second or third trimester of gestation, or head trauma during birth, or some other event early in brain development interacts with later brain maturation with the net result of developmental pathology. The second type of models concentrates on peri-adolescent development attempting to account for the adolescent or early adulthood onset of schizophrenia. For example, Feinberg (1982) proposed that brain pathology in schizophrenia might be a result of excessive pruning during adolescence, the time when brain undergoes substantial changes, due to a faulty genetic programming. The third type of models posits neurodegenerative course of schizophrenia due to an active morbid process, of which acute psychosis is a reflection (Kraepelin, 1919; Loebel et al., 1992). All of these models have support from the empirical research, although evidence for neurodegenerative model is more controversial than for the other two models (see Heckers, 1997 for a review). Specifically, the evident lack of gliosis in post-mortem studies of schizophrenia patients is usually cited against the neurodegenerative model of schizophrenia. However, studies of the effect of N-Methyl-D-aspartate (NMDA) blockade in the rat showed that when a high percentage of the neuronal population in the posterior cingulate cortex is destroyed by treatment with NMDA antagonist drugs, which induce neurotoxic excitation in the cerebral and limbic cortices if administered

chronically, there is a transient increase in the markers of two types of glia, but these return to normal after some time (Fix et al., 1995). Thus, the common finding that structural reductions in schizophrenia are not associated with evidence for gliosis might mean either developmental abnormalities early in life or neurotoxic degeneration in adulthood, with these alternatives not being mutually exclusive (Olney, Newcomer and Farber, 1999).

Keshavan (1999) has advanced a 'three hit' model of schizophrenia pathogenesis, which integrates three alternative models: pre-natal neurodevelopmental, peri-natal/adolescent neurodevelopmental, and neurodegenerative. This model synthesises evidence for adverse events and markers at different time points in brain development and after the illness onset in individuals manifesting schizophrenia. It posits that there are critical 'windows of vulnerability' in brain development, and that adverse events during the first of them, i.e. pre-natal brain genesis, may lead to a cascade of abnormal events in brain maturation that would result in early dysplasia, abnormal pruning during adolescence, and further neurodegenerative processes related to the disease progression.

2.3. Cognitive Deficits

Discovery of antipsychotics in the 1950s revolutionised the treatment of schizophrenia and shifted the emphasis from cognitive deficits onto positive symptoms, which conventional antipsychotics so dramatically reduce. However, by the 1960s it became obvious that reduction in positive symptoms did not lead to recovery from schizophrenia and did not improve functional outcome significantly (Hegarty et al., 1994). The understanding of what is a fundamental deficit in schizophrenia made a full circle, with acceptance once again of what Kraepelin and Bleuler suggested at the dawn of the 20th century. Cognitive deficits are a core feature of schizophrenia, which i) precipitate the psychotic and negative symptoms in the aetiology of the disease (e.g. Weickert and Goldberg, 2000); ii) relatively stable over time with progressive deterioration after the age of 65 in some patients (e.g. Friedman et al., 2001); iii) persist upon the remission of psychotic symptoms (e.g. Heaton et al., 2001); iv) are related to but separate from negative symptoms (e.g. Harvey et al., 1996; Hughes et al., 2003). Most importantly, cognitive deficits are of a greater importance than positive or negative symptoms in predicting functional outcome, such as work status, activities of daily living,

community outcome, social problem solving and skill acquisition (review, Green, 1996).

Schizophrenia is considered to be one of the most expensive psychiatric disorder to treat (Capri, 1994; Knapp, 1997). Functional impairment is one of the greatest contributors to the cost of the illness (Kenny and Meltzer, 1991). Cognitive domains that were linked to different aspects of functional outcome are working memory, executive function, attention, verbal learning and memory, verbal fluency, and fine motor function (Green, 1996; Green et al., 2000).

2.3.1. Working memory

2.3.1.1. The definition of working memory

Working memory function is hypothesised to be sustained by a network of temporary (as opposed to long-term) memory systems. It plays a crucial role in many cognitive tasks such as reasoning, learning and understanding. Working memory refers to the ability to hold the stimuli of different sensory origin, either of external or internal origin (e.g. sensory input or imagery), 'on line' for a short period of time (a few seconds) and then either to use it directly after a short delay or to process and/or manipulate it mentally in some way before use in order to solve cognitive and behavioural tasks of different complexity. Thus, working memory involves active rehearsing, processing and manipulation of information. It is most engaged when the information is new or not well learned or the task to be solved is novel with hight cognitive demands and has not reached the level of automaticity.

2.3.1.2. Working memory models

The classic model of working memory was described by Baddeley (1986). In this model, working memory refers to a single limited-capacity system that consists of three elements: two 'slave' systems that retain and process the stimuli and an attentional system that supervises and coordinates two 'slave' systems. The 'slave' systems are the articulatory or *phonological loop*, which processes speech-based stimuli, and *visuospatial sketchpad*, which processes visuospatial stimuli.

Others have argued against the notion of a single system and proposed instead the existence of relatively independent subsystems for different sensory modalities and the tasks of different nature (e.g. Allport, 1980; Barnard, 1985). Although the theoretical debate is not relevant for the present purposes, it is interesting to note

that whatever theory one considers, the process that is referred to as central executive in Baddeley's model is common to all and seems to depend on the function of prefrontal cortex (PFC) (Goldman-Rakic, 1995). The abnormal function of the PFC will affect the working memory function, whether it is sustained by a single system or a network of subsystems, as they all converge on the PFC at some point along the process for attentional/controlling aspect.

2.3.1.3. The nature of working memory dysfunction in schizophrenia

The PFC, especially the dorsolateral part, is implicated in working memory (e.g. Goldman-Rakic, 1999). The pattern of activation of this region in schizophrenia patients during complex working memory tasks is suggestive of a system that is of more limited capacity than in normal individuals (review, Manoach, 2003; new evidence, Jansma et al., 2004).

Neuropsychological studies that assessed working memory function in schizophrenia patients have observed an impairment of each component of the working memory system, i.e. the phonological loop, the visuo-spatial sketchpad and the central executive (e.g. Stuss et al., 1982; Keefe et al., 1995, 1997; Pantelis et al., 1997). Although the relative degree of the impairment of each component is unclear, the crucial pattern is that the tests that involve more than one component and/or more complex produce differentially greater severity of impairment in patients relative to normal controls. This pattern of results confirms the findings from imaging studies suggestive of a working memory system that is of more limited capacity than in healthy individuals.

Patients with schizophrenia were found to be more impaired on working memory function than patients with frontal or temporal lobe lesions, matched for age, sex, and premorbid intellectual ability (IQ) as measured by National Adult Reading Test (NART) (Pantelis et al., 1997). Schizophrenia patients have showed worse use of strategies on working memory task as compared to other patients, suggesting that the impairment in executive function (see below for a definition) may underlie the working memory impairment in schizophrenia. However, one might argue that if the central executive capacity of the working memory system is more limited in individuals with schizophrenia than in other populations, this will impede the successful use of strategies on a working memory task even if there is no dysfunction in executive function *per se*. Thus, it is not always easy to distinguish between two alternatives to account for poor working memory, i.e. the system of a more limited capacity vs. inadequate use of strategies. The evidence points to the

impairment of both; therefore, it is likely that both factors contribute to working memory deficit in schizophrenia.

Working memory deficit is more severe than the deficits in some aspects of long-term memory in schizophrenia patients. Performance on verbal working memory was found to be 4 SDs below the normal mean, while the performance on long-term memory as measured by recognition was only 1 SD below the normal mean (Sullivan et al., 1997). Recognition memory does not require any strategic processing of the information. This finding might mean that although passive learning can be relatively preserved in schizophrenia, more complex learning that requires active and strategic processing of the information might be impaired due to the deficit in working memory function. In fact, it was found that deficits in strategic long-term memory (free recall, memory for temporal order and self-ordered pointing) could be accounted for by the deficits in working memory (Stone et al., 1998). The fact that working memory deficits can cause impairment in long-term memory will have an implication for the learning of new and complex skills and have a consequence for the functional outcome.

2.3.1.4. Relationship between working memory and symptoms

The working memory impairment is thought to associate with formal thought disorder. As monitoring one's own speech is one of the functions of working memory, the individual with gross impairment in this function might find it difficult to remember the original intention of the sentence one has just spoken. The speech of such an individual might be potentially filled with loose associations and derailment (Rochester, 1978). Indeed, visuo-spatial working memory impairment has been found to significantly correlate ($r = 0.52$) with formal thought disorder (Spitzer, 1993).

One of the functions of working memory is to keep track and retain the information about the origin of the stimuli, i.e. external vs. internal. Frith and Done (1989) has put forward an interesting suggestion that some of the positive symptoms of schizophrenia might be due to the failure to monitor the initiation of self-generated thoughts. These positive symptoms might include thought insertion, delusions of control, auditory and visual hallucinations. Empirical findings suggest that this indeed might be the case. It was found that schizophrenia patients are worse than healthy people in monitoring the source of self-generated information, but similar to normal people at monitoring the information perceived from visual or auditory sources. Moreover, patients with auditory hallucinations were more impaired on source monitoring than patients without these symptoms (Keefe et al., 2001).

Keefe (1998) has hypothesised that working memory deficit might underlie one's inability to identify self-generated mental content, referred to as 'autonoetic agnosia'. However, the relationship between working memory deficit, autonetic agnosia and positive symptoms has not been studied directly.

Working memory is also associated with negative symptoms. The pattern of the findings suggests that the dysfunction of working memory might cause some of the negative symptoms such as lack of motivation, rather then other way around. Thus, in the study of working memory that used pupil size as a measure of effort put into a performance on the task, it has been concluded that working memory deficit can not be accounted for by reduced motivation (Granholm et al., 1996).

2.3.2. Executive function

2.3.2.1. The definition of executive function

Executive function refers to a set of cognitive abilities that are required for a goal-directed behaviour and adaptation to a range of environmental changes and demands (Loring, 1999). These include the ability to plan and to anticipate outcomes; to use abstract concepts in order to work out and to execute the strategies for problem solving whilst monitoring one's actions and their impact, and to adjust one's responses according to feedback. Executive skills are most important for dealing with novel and/or complex situations. In essence, executive function is involved in controlled and goal-oriented behaviour as opposed to reflexive or automatic one. Physiologically, executive function is linked to frontal lobes but is not confined to them, as there is a growing awareness of the importance of cortical-subcortical circuits in frontal functions (e.g. Cummings, 1993; Jones, 1997; Pantelis et al., 1997).

There is a conceptual overlap between the central executive of working memory model and executive function. However, these two concepts are separate, although closely interlinked. Executive function refers to the temporally more extended process than the central executive. The central executive refers to the ability to hold and manipulate information on-line for the short periods of time, whereas executive function refers to one's ability to solve problems and conduct goal-directed behaviour over extended periods of time. Although theoretical differences between two concepts are apparent, both processes depend heavily on attention resources. This led some researchers to argue that it is very difficult to distinguish between two processes in reality. In fact some of the tasks, such Tower of London,

Wisconsin Card Sorting Task (WCST), or Trail Making form B, have been used to measure working memory or executive function processes by different researchers (e.g. Goldberg et al., 1990; Braff et al., 1991; Pantelis et al., 1997; Moritz et al., 2002; Pukrop et al., 2003).

2.3.2.2. Tests of executive skills

There are many tasks that are used to measure executive function, such as Trail Making Test, the Category Test, the Stroop Colour Word Test, Tower of London/Hanoi/Toronto tasks and WCST mentioned earlier. These tests measure different executive skills. Trail Making Test, form B (Reitan and Wolfson, 1993) tests, amongst other skills, the ability to rapidly switch between processing two types of stimuli (mental flexibility). The Category Test (Reitan and Wolfson, 1993) requires the ability to think abstractly, derive hypotheses and test them while adjusting one's performance in response to the feedback. The Stroop Colour Word Test (Stroop, 1935) requires the inhibition of pre-potent automatic response, which is considered to be one of the roles of the executive function in controlling behaviour. Tower tasks test planning ability for the optimal rout to reach the goal by holding different options in mind and choosing the best one by comparison. Finally, WCST (Heaton, 1993) is similar in its demands to the Category Test by requiring subject to form abstract concepts in regard to the stimuli, to generate hypotheses for the problem solving and to shift strategies in response to the feedback.

2.3.2.3. The nature of executive dysfunction

As early as Kraepelin, it was recognised that schizophrenia involves disturbances in executive function skills. Since executive dysfunction in schizophrenic patients resemble certain aspects of behavioural problems of people with 'frontal lobe' syndrome, schizophrenia was even considered to be a frontal lobe disorder.

Schizophrenia patients show deficits on most measures of executive function when compared to healthy individuals (e.g. Fey, 1951; Goldberg et al., 1990; Braff et al., 1991; Perlstein et al., 1998). This suggests that the executive skills that are tapped by the tasks either: (i) are not developed to the same extent as in healthy controls and thus might present a neurobiological vulnerability; or (ii) have been damaged by the disease process and/or medication.

Long-term treatment with typical antipsychotics have not been found to have either beneficial or detrimental effect on executive function (e.g. Cassens et al., 1990) and in lower doses was found to have beneficial affect on attentional aspect

of executive function as measured by the Stroop test (Harris et al., 1997). These findings suggest that in chronic patients treated with neuroleptics over a period of time deficits in executive function cannot be attributed to the effect of medication.

The studies that attempted to discriminate between the alternatives (i) and (ii) have produced inconclusive results. Some of the investigators have found deficits in executive function (usually measured by WCST) in first-degree relatives (e.g. Franke et al., 1992; Sharma et al., 1999) or those with schizotypal personality disorder (Trestman et al., 1995), suggesting that the deficits in executive function might be a neurobiological factor rather than the consequence of the illness. However, the evidence to support this conclusion is not robust at the present, since others have not corroborated these findings (Battaglia et al., 1994; Stratta et al., 1997). It is likely that there is a state (associated with symptoms, medication, etc.) as well as a trait (residual deficit even after effective treatment, and as found in unaffected relatives) component to the executive dysfunction in schizophrenia.

2.3.2.4. Relationship between executive dysfunction and symptoms

The degree of executive dysfunction is associated with some symptoms, but not others. Positive symptoms, such as hallucinations and delusions, have almost no correlation with the severity of executive dysfunction (Franke et al., 1992; Morris et al., 1995; Voruganti et al., 1997), whereas the severity of negative symptoms, such as affective flattening, alogia, social withdrawal or avolition, correlate with poor performance on executive function measures (e.g. Rossi et al., 1997; Voruganti et al., 1997). However, one study of unmedicated young acute females with schizophrenia (Parellada et al., 2000) has found WCST performance deficits to associate with both positive and negative symptoms.

Performance on WCST has also been found to correlate with the lack of insight of illness (e.g. Young et al., 1993; Voruganti et al., 1997). Unawareness of illness has been shown to correlate with poor medication compliance (Garavan et al., 1998), self-injurious behaviour (Meltzer, 2001), and with the risk of violence directed towards others (Arango et al., 1999). Several studies have suggested that unawareness of illness may be specifically linked with executive impairments and not with other cognitive deficits such as attention or memory (e.g. Lysaker et al., 1998; Rossell et al., 2003; but see Marks et al., 2000). Thus, executive dysfunction can lead to a poor outcome by predisposing an individual with schizophrenia to the failure to comply with the treatment as well as violent behaviour towards oneself and others.

2.3.3. Attention

2.3.3.1. The definition of attention

Attention refers to a set of operations that enable the organism to detect, recognise, and identify relevant stimuli in the environment. Selective attention refers to the ability to focus on the stimulus ignoring the rest of the sensory input as well as internally generated content. Sustained attention (or vigilance) refers to the ability to focus on the stimulus over a period of time or until the processing of it is complete.

2.3.3.2. The nature of attention deficit

Both Kraepelin and Bleuler have emphasised disturbances in attention as a core deficit in schizophrenia. Inability to sustain attention over a period of time (distractibility) as well as inability to attend selectively to one stimulus while reducing the salience of others (overinclusiveness) can lead to sensory overload and predispose one to the experiences that patients with schizophrenia describe. The phenomenological descriptions of these experiences by patients often have reference to being overwhelmed by the environment where every stimulus has a perceptual and/or emotional salience, importance and meaning. It has been hypothesised that this overwhelming sense of importance and meaning about even most banal events can lead to a development of delusions, the purpose of which is to make sense of these subjective experiences (Hemsley, 1998).

Some contemporary researchers identify deficits in attention and information processing as 'central' to the disorder (e.g. Braff, 1985). Indeed, deficits in attention theoretically can underlie deficits in other higher cognitive functions such as working memory and executive function. There have been a multitude of studies investigating attentional processes, both controlled and automatic, in schizophrenia using neuropsychological and psychophysiological (e.g. pre-pulse inhibition of the startle response (e.g. Kumari et al., 1999, 2000, 2002b, in press), eye movements (e.g. Solomon et al., 1987) methods.

The pattern of the findings in schizophrenia patients suggests that poor performance on the measures of attention is not due to the failure to allocate attention, indicating that the executive control of attentional function is not impaired. For example, while patients with schizophrenia deteriorate more than healthy individuals when asked to perform multiple cognitive tests in divided attention studies, they appear to utilize normal processing strategies.

Furthermore, the findings suggest that the attention deficits are related to sustained and selective attention processes and are not simply due to excessively slow processing (review, Cadenhead and Braff, 2000).

Perhaps more than any other aspect of cognitive functioning, attentional deficits are strong candidates as markers of vulnerability. Attentional deficits were shown to be persistent in patients with schizophrenia who were largely in remission of their symptoms (e.g. Nuechterlein et al., 1986). Children and unaffected relatives of schizophrenia patients, as well as individuals with schizotypal personality disorder show deficits in both sustained and selective attention widely replicated across studies (e.g. Cornblatt and Erlenmeyer-Kimling, 1985; Erlenmeyer-Kimling et al., 1989; Green et al., 1997; Young et al., 1998).

2.3.3.3. Relationship between attention deficits and symptoms

Attention deficits have been found to associate with deficit syndrome and its persistent (primary) symptoms, such as restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive (e.g. Thaker et al., 1988; Ross et al., 1997). Schizophrenia patients who are highly distractable (i.e., have poor ability to focus and sustain attention) have been found to have higher levels of formal thought disorder (e.g. Cornblatt et al., 1985; Perry and Braff, 1994; Solomon et al., 1987). The association between attentional dysfunction and positive symptoms (hallucinations and delusions) has also been demonstrated (Cornblatt et al., 1985). The relationship of attentional dysfunction with all three- symptom dimensions reinforces the view that attentional impairment is at the core of schizophrenia.

2.3.4. Learning and memory

2.3.4.1. The definition of learning and memory

The human memory system is complicated and multifaceted. There are many components of this system, with many different ways to conceptualise memory performance. The common subdivisions of the memory system focus on both the type of information to be learned and remembered, e.g. general knowledge vs. autobiographical facts, as well as the duration of storage of the information, e.g. short-term vs. long-term. Short-term memory concept is intrinsically linked with the concept of working memory, discussed earlier in the chapter. In this section, the function of long-term memory and learning will be discussed.

2.3.4.2. The nature of memory and learning impairment

Deficits in memory and learning are not homogeneous and differ in their severity across different components of memory system. Some of the impairments are so severe that they have been said to present a differential deficit, while other memory and learning functions have been found to be relatively preserved as compared to healthy people and to be least impaired as compared to other cognitive domains deficient in schizophrenia.

Episodic memory, the ability to learn and recall information from previously experienced events (Tulving, 1983) has been proposed to present a differential deficit in schizophrenia (e.g. Gold et al., 1992). One study (Saykin et al., 1991) of medication free and medication naïve patients used a profile analysis of the cognitive impairment and demonstrated that memory function was more severely impaired than other cognitive functions such as attention, executive function, language, spatial abilities, sensory and motor functions. This pattern of findings was confirmed with a sample of first-episode neuroleptic-naïve patients (Saykin et al., 1994), showing that this differential memory impairment cannot be accounted by the effect of neuroleptic or anticholinergic medication. More recently, Toulopoulou and colleagues (2003) reported differential impairment in verbal memory as measured by the recall on Logical Memory tasks, both immediate and delayed, in both schizophrenia patients and their relatives, suggesting that dysfunction in verbal memory might present familial, presumed genetic, liability to schizophrenia.

It is noteworthy that in the study by Saykin et al. (1994) the only other area of severe impairment was sustained attention as measured by the CPT. Theoretically, attention and memory are very closely interlinked. Failure in selecting the stimuli for further processing and storage will inevitably lead to poor learning of the information and thus failure of memory. Equally, executive component of working memory might play an important intermediate role in the process of information acquisition. Poor encoding strategies will lead to attentional overload and thus to the disruption of the encoding of the information, which subsequently will result in poor learning and memory. Thus, although memory impairments can be differentially severe in schizophrenia, this does not undermine the significance of the impairment in other domains, as different domains are intimately interlinked. Therefore, even a modest disruption in one can lead to a relatively greater disruption in the others.

Indirectly confirming this theoretical notion is the fact that memory problems in schizophrenia are not due to rapid forgetting, but due to encoding and retrieval deficits, since recognition deficits in patients are mild (e.g. Paulsen et al., 1995), suggesting that the information storage in schizophrenia is relatively intact. Furthermore, schizophrenia patients have been directly shown to be impaired in the encoding of the information (e.g. Gold et al., 1992). When read a story or a list of words, they learn less than healthy individuals even after the presentation is repeated, showing a reduced "learning curve". On the retrieval side, schizophrenia patients appear to recall less information than healthy individuals when they are asked simply to reproduce the information previously learned without cues or prompts (free recall) (e.g. Paulsen et al., 1995). This recall failure remains even when the reduced learning rate is accounted for. Furthermore, schizophrenia patients benefit less from prompted and cued recall than healthy individuals. They are also less able to use semantic structure embedded in the information to aid the encoding and the retrieval of the information (e.g. Kareken et al., 1996). This is not simply due to the lack of strategy use. Even when patients are instructed to cluster the information (e.g. by categories), they still do not benefit from the embedded structure in the information to be recalled. This failure to utilise a clustering strategy was found to be the primary explanation of encoding and retrieval problems (e.g. Iddon et al., 1998) and has been attributed to impaired executive aspects of working memory (Goldman-Rakic, 1994).

The failure to use encoding strategies has been also linked to the disruption of semantic system functioning, which might be the consequence of the learning process where the information is acquired without any organisational structure at the time of encoding and storage. Impairment of semantic memory has been repeatedly reported in schizophrenia patients (Kareken et al., 1996; McKay et al., 1996; Aloia et al., 1998; Goldberg et al., 1998). The level of semantic memory deficits in schizophrenia was found to match that of the patients with Alzheimer's dementia (McKay et al., 1996).

This semantic memory impairment may have a consequence for the information access. Thus, one of the tasks used to assess semantic memory requires a subject to generate a list of word using first a phonological principal (i.e. words starting with 'F') and then semantic principle (i.e. words belonging to the category 'animals'). In healthy individuals, semantic fluency exceeds the phonological fluency, i.e. they give more responses to a semantic cue rather than a phonological one. In subgroup of patients with schizophrenia these pattern is reversed and this

lack of semantic fluency is associated with the presence of sever formal thought disorder (Goldberg et al., 1998).

Studies that used other methods of assessing semantic memory in schizophrenia, such as word associations, priming effect and analysis of the verbal output have also found abnormalities in the structure of semantic memory in schizophrenia patients as compared to normal controls (review, Spitzer, 1997). As has been discussed above, this structural impairment of semantic memory may have consequences for both encoding and retrieval of knowledge.

Other aspects of learning and memory are not impaired to the same extent as semantic or episodic memory. Thus, deficits in procedural learning, the ability to learn skills and motor acts, are relatively mild (e.g. Goldberg et al., 1993). There is some uncertainty as to what extent the impairment in procedural learning is inherent to the disease process and to what extent it is impaired by the treatment, since it has been shown to be affected by the treatment with neuroleptic medication (Bedard et al., 1996, 2000). Studies indicate that both might have play a role, as patients with schizophrenia on conventional antipsychotics show slower rates of motor learning than medication-naïve patients (Purdon et al., 2003), while medication-naïve patients show poorer procedural memory than normal controls (e.g. Scherer et al., 2003).

2.3.4.3. Relationship between memory & learning and symptoms

Goldberg and colleagues (1993) examined different aspects of memory and learning, including semantic, episodic and procedural, in monozygotic twins discordant for schizophrenia and found an inverse relationship between verbal episodic memory (memory for stories) and negative as well as positive symptoms. Heydebrand and colleagues (2004) studied correlates of cognitive deficits in first episode schizophrenia patients and observed the relationship between the severity of negative symptoms and general psychopathology symptoms and memory impairment, as measured by a summary index which included scores on both verbal and non-verbal episodic memory tasks. Bruder et al. (2004) have reported that patients with deficits in both verbal and spatial memory had greater negative symptoms severity than patients with only verbal memory deficit. Rushe and colleagues (1999), however, observed no relationship of either negative or positive symptoms with verbal or non-verbal episodic memory and learning in chronic schizophrenia patients. Finally, both verbal and non-verbal memory deficits were

found to be associated with greater severity of thought disorder (Nestor et al., 1998).

2.3.5. Psychomotor function

2.3.5.1. The definition of motor function

Psychomotor function is defined as pertaining to the motor effects of psychological processes. Psychomotor tests are tests of motor skill which depend upon sensory or perceptual motor coordination. The most widely used measures of psychomotor function in schizophrenia research are the tests of fine motor function, such as finger tapping test (FTT) and grooved peg board (GPB). FTT assesses psychomotor speed, whereas GPB assesses dexterity.

2.3.5.2. The nature of psycomotor dysfunction

Compared with other cognitive processes, relatively less attention has been focused on psychomotor functioning in schizophrenia (Walker et al., 1999), even though some of the earlier precursors of schizophrenia spectrum disorders are disturbances in motor functioning (e.g. Fish et al., 1992; Neumann and Walker, 1995; McNeil and Cantor-Grace, 2000). Dysfunctions in motor functioning, particularly psychomotor speed and dexterity, are consistently seen in adults with schizophrenia (e.g. Saykin et al., 1994; Bilder et al., 1995). Cannon et al (1999) found that motor dysfunction at the age of 4 was a significant predictor of an adult schizophrenia diagnosis. It is unlikely to be of genetic origin, since it is one of the deficits differentiating monozygotic twins discordant for schizophrenia (Golderg et al., 1990; Suddath et al., 1990). There is a growing body of literature suggesting that motor dysfunction in schizophrenia is associated with social and emotional disturbances (e.g. Fish et al., 1992; Dworkin et al., 1993; Neumann et al., 1995; Walker et al., 1996). It is also associated with the deficits of higher cognitive processes. D'Reaux et al. (2000) found the motor functioning assessed with the finger-tapping test (FTT) was strongly positively correlated with attention/working memory performance in healthy adults and patients with schizophrenia. More recently, Silver and Shlomo (2001) observed an association between motor functioning and the ability to identify facial emotional expressions in schizophrenia patients. Finally, motor function, particularly dexterity, has been found to predict rehabilitation success in patients (Weaver and Brooks, 1964). Licher and Cummings (2001) proposed that motor, cognitive, and emotional disturbances in schizophrenia arise due to subcortical basal ganglia dysfunction. In summary, psychomotor dysfunction is a prominent feature of schizophrenia, which is associated with other cognitive, social, and emotional disturbances.

2.3.5.3. Relationship between motor function and symptoms

Psychomotor dysfunction is consistently associated with negative symptoms. There are a strong positive correlation between motor deficits and withdrawn behaviour (Baum and Walker, 1995) and an inverse correlation with anxiety/depression (Dworkin et al., 1993; Neumann and Walker, 1995; Walker et al., 1996). Slower finger tapping was associated with an increase in disorganized symptoms in a longitudinal study of cognitive function in first-episode and recent-onset schizophrenia patients by Gold et al. (1999). The presence of motor dysfunction early in the illness is associated with the emergence of tardive dyskenisia later in the disease process (Cliquiri and Lorh, 1994).

2.3.6. Summary of cognitive deficits

Patients with schizophrenia show deficits across a large number of neurocognitive domains. Overall performance deficit can be between 1.5 and 2 SDs below the normal population mean (Bilder et al., 1995). Some of the cognitive domains tend to differentiate between patients and healthy controls more reliably than others. These include working memory, learning and memory, executive function, language skills, attention, and psychomotor function (e.g. Bilder et al., 1994; Saykin et al., 1991, 1994; Riley et al., 2000). Amongst these domains, verbal learning and memory might present a differential impairment with up to 3 standard deviations below the normal performance levels (Saykin et al., 1991; 1994). The impairment of verbal learning and memory has been linked to the disruption of normal semantic system structure in schizophrenia, the indirect evidence of which has been repeatedly observed in schizophrenia patients (Kareken et al., 1996; McKay et al., 1996; Aloia et al., 1998; Goldberg et al., 1998). Overall, schizophrenia patients show much more severe impairments on the tests of higher cognitive function that require cognitive control and active information processing for the optimal performance. Tests of perceptual discrimination, implicit memory, procedural learning or recognition memory do not reliably differentiate patients with schizophrenia from healthy individuals (e.g. Goldberg et al., 1993; Bilder et al., 1995).

2.4. Theories Relating Structural Alterations to Cognitive Dysfunction in Schizophrenia

Cognitive deficits characteristic of schizophrenia are generally conceived to be a manifestation of brain pathology. Kraepelin proposed that schizophrenia is a disease of the frontal lobes (Kraepelin, 1919). The integrity of the frontal lobes and particularly prefrontal cortex is associated with higher cognitive functions such as executive control, planning, decision making, goal-directed behaviour, selective attention, working memory; all of which have been shown to be disrupted in schizophrenia (review, Elvevag and Goldberg, 2000).

The most influential model linking frontal lobe abnormality to psychopathology and cognitive deficits in schizophrenia was proposed by Goldman-Rakic (1995; 1999; Goldman-Rakic and Selemon, 1997). The model considers the prefrontal cortex to be the primary site of schizophrenia pathology that would affect working memory in particular. According to the model, the failure of working memory might underlie negative symptoms, behavioural disorganisation, formal thought disorder and cognitive deficits such as executive function, conceptual thinking and memory formation.

Pearlson and colleagues (1996) proposed that schizophrenia is a disease of heteromodal association cortex. They suggested that dynamic interrelationships between the regions of heteromodal association cortex, including dorsolateral prefrontal cortex, heteromodal regions of superior temporal gyrus, inferior parietal lobule, limbic system and basal ganglia, as well as normal neocortical left/right asymmetry might be neurodevelopmentally disrupted in schizophrenia leading to its cognitive and symptomatic features.

Crow (1989, 1990, 1995) has stressed decreased left/right asymmetry in the temporal lobe of schizophrenia patients and proposed that this developmental abnormality has a genetic component related to the evolution of language in the human species. The failure to develop normal brain asymmetries is hypothesised to underlie schizophrenia phenotype and lead to cognitive (particularly that of language) and symptomatic disturbances characteristic of schizophrenia.

Other models concentrate on inter-connections and inter-relationships of function between the prefrontal cortex, temporo-limbic cortex (particularly hippocampus),

and the ventral striatum, as well as dopaminergic transmission within the ventral striatum to account for schizophrenia phenotype (Buchsbaum, 1990; Carlsson and Carlsson, 1990; Grace, 1991; Gray, 1995; 1998; Csernansky and Bardgett, 1998; O'Donnell and Grace, 1998). Models that have implicated fronto-striatal and limbic-striatal networks vary in detail but have one common feature. All of these models draw on reduced glutamatergic input from prefrontal cortex and hippocampus to the ventral striatum, which results in changed dopaminergic transmission in nucleus accumbens. While abnormalities in hippocampus and prefrontal cortex are proposed to account for cognitive disturbances, dopaminergic upregulation within nucleus accumbens is suggested to lead to the emergence psychotic features of schizophrenia. Some of the researchers extended their models to include ventrostriatal-thalamic and thalamo-cortical circuits that would be disrupted as a consequence of the primary abnormalities in glutamatergic and dopaminergic transmission within ventral striatum (Gray, 1995; O'Donnel and Grace, 1998). Jones (1997) proposed that the cell loss in the thalamus itself, either as a primary pathology or as secondary to cortical or other subcortical pathology, could lead to disintegration of thought processes due to the failure of the thalamus to induce oscillation of large ensembles of cortical and thalamic neurons necessary for the binding of the brain states in functionally integrated manner.

Weinberger and Lipska (1995) stressed the importance of prefrontal-temporolimbic communication for understanding the nature of schizophrenia phenomenology. According to this model, nucleus accumbens is important in schizophrenia only within the context of being a site of convergence between prefrontal and hippocampal regions. Prefrontal-hippocampal intra-cortical projections as well as Papez circuit (Papez, 1937) are two other main routes of prefrontal-temporolimbic connections. Dysfunctional prefrontal-temporolimbic connectivity along any of these three main routes will result in 'noisy' or 'missinformed' communication between prefrontal and limbic cortices leading to disintegration of normal function. Dopaminergic transmission might not be abnormal *per se*, but rather will be evoked in exaggerated and/or contextually inappropriate manner leading to increased reaction to stress and vulnerability to psychosis.

Graybiel (1997) proposed a model that focuses on basal ganglia and parallel neuronal circuits that connect them with the neocortex, including efferents from prefrontal cortex to caudate nucleus, motor cortex to putamen, and limbic cortex to nucleus accumbens. The primary role of the basal ganglia in behaviour is the generation of cognitive patterns or templates for action that involve thought, movement and emotion within these three cortical-basal circuits respectively.

Dysfunction of basal ganglia due to a structural and/or neurochemical abnormality would lead to the disturbance of these processes, resulting in cognitive, negative and psychotic features of schizophrenia due to an abnormal function of caudate, putamen or ventral striatum respectively.

Andreasen and colleagues (1996; 1998) proposed the 'cognitive dysmetria' model of schizophrenia, which concentrates on connectivity between prefrontal cortex, thalamic nuclei, and the cerebellum. This cortico-cerebellar-thalamo-cortical circuitry (CCTCC) was proposed to have a role in the coordination of both motor and cognitive processing (Schmahmann, 1991; 1997; Middleton and Strick, 1994). A disruption in the function of this circuitry would result in deficient processing, prioritising, retrieval, coordination, and responding to information, i.e. 'cognitive dysmetria', which according to this model is the fundamental deficit of schizophrenia underlying its broad variety of symptoms.

To summarise, most of the theoretical models of brain pathology in schizophrenia implicate the prefrontal cortex as one of the areas that underlie cognitive and clinical features of schizophrenia. However, the prefrontal cortex does not function in isolation, and thus all models emphasise the role of the neuronal circuitry connecting prefrontal cortex with other cortical and sub-cortical structures to account for the multitude of disrupted cognitive processes in schizophrenia. Moreover, the prefrontal cortex does not have to be structurally altered in order to exhibit functional disruption, as primary abnormalities in other brain regions might result in hypofrontality as a secondary pathology.

2.5. Review of the Studies Investigating Structure/Cognition Relationships

A literature search, using the PubMed electronic journal engine, and manual library search for the relevant publications since 1990, as well as searching the reference lists of the retrieved articles, revealed 36 MRI studies examining structure/neurocognition relationships in first-episode and chronic schizophrenia patients, using ROI approach and utilizing methods of image processing and analyses that became available in the early 1990s. Most studies used volumetric measurements, whereas other studies (Raine eta l., 1990; Colombo et al., 1993; Di Michele 1992; Raine et al., 1992; Rossi et al., 1994; Woodruff et al., 1997a) used area or/and width measurements. Since area or width of a structure is a

reflection of its volume, these studies were also included in the review. One study (Saldago-Pineda et al., 2003) has applied VBM to investigate the relationship between regional grey matter concentration and the performance on sustained attention task (CPT), in addition to the manual ROI volumetric measurement of the thalamus and its association with sustained attention deficit. Since concentration and volume in the VBM context measure different indices of regional brain tissue availability (see *section 2.2.1. Methods of quantifying structural alterations for more detail*), only the findings pertaining to the volumetric ROI part of the analysis are included in the review in the relevant section (i.e. Thalamus) to make the results of the reviewed studies comparable with one another. The coverage of the tissue concentration/neurocognition findings is postponed until *Chapter 7* (Experimental Study 3).

Most studies had a control group. All studies adopted a correlational design, with the exception of three early studies, two of which investigated whether the certain structures were altered in the group of patients with specific cognitive deficits (Raine et al., 1992; Colombo et al., 1993), and one study (Raine et al., 1990) which examined structural and function characteristics of the corpus callosum, but did not correlate structural and neurocognitive variables (see *Table 2.1* for the summary of the main findings).

One way to structure this review would be by cognitive function. However, as different studies have used different neuropsychological tests to measure the same cognitive domain, and, conversely, the same tests were used to measure different domains, this approach seemed cumbersome, requiring arbitrary decisions about attributing neuropsychological measures to cognitive domains. The review, therefore, is organized by brain structures, with the view of a particular structure in terms of the 'node' within the distributed functional neuronal network(s). In order to address two distinct but related issues, namely i) which structural abnormalities are associated with cognitive deficits in schizophrenia; and ii) whether structure/function relationships seen in normal individuals are altered in schizophrenia patients, the findings on the integrity of the structural volumes in patients for each brain region, where they were available, are presented in addition to examining and comparing the structure/function relationships in patients and controls (the information on cognitive deficits can be found in *Table 2.1*). Not only the studies that have found structural volumes to be altered have been included, but all studies that have investigated structure/function relationship. The reason for this is that if the relationship existed in the absence of statistically significant morphological differences between the groups, the exclusion of these findings will

result in the loss of information, since the differences might still pertain to at least a sub-group of patients.

The review commences with whole brain volume, followed by ventricular size, frontal lobe, temporal and medial temporal lobes, planum temporale, parietal and occipital lobes, basal ganglia, cerebellum, midbrain, and brain asymmetries. Almost all studies, unless testing a very specific hypothesis, have measured more than one region of interest, and thus appear in more than one section, with cross-references between the sections. *Table 2.2* presents the reviewed studies clustered by structure.

TABLE 2.1. Reviewed studies of MRI/Neuropsychological relationships

NOTE: Studies are entered in descending order by the recency of publication. All subjects were right-handed unless otherwise specified in the table. Only data for MRI and NP variables are presented, excluding data for symptoms, demographics and medical history. All patients were on conventional neuroleptics unless otherwise specified in the table. All studies used 'Region of Interest' approach. The names for the cognitive domains are retained as used in the corresponding publication.

ABREVIATIONS: **ANT** = Animal Naming Test; **BNT** = Boston Naming Test; **BG** = basal ganglia; **BSRT** = Buschke Selective Reminding Test; **C** = controls; **CF** = cognitive flexibility; **COWA** = Controlled Oral Word Association; **CVLT**=California Verbal Learning Task; **DLPFC** = dorso-lateral prefrontal cortex; **DMPFC** = dorsomedial prefrontal cortex; **DST** = Digit Symbol Test; **EF** = executive function; **F** = female; **FEP** = first episode patients; **FT** = finger taping task; **GMV**= grey matter volume; **GP** = globus pallidus; **GPB** = grooved peg board; **Hippo** = hippocampus; **L** = left; **LM** = logical memory (**I** and **II** = immediate and delayed); **LV** = lateral ventricle; **M** = male; **Mem** = memory; **MF** = motor function; **M-WCST** = Modified version of Wisconsin Card Sort (unambiguous card sorting); **NART** = National Adult Reading Test; **NC** = normal controls; **NP** = neuropsychological; **OFC** = orbitofrontal cortex; **P** = patients; **PHG** = parahippocampal gyrus; **PFC** = prefrontal cortex; **PLS** = Partial Least Square; **R** = right; **SAD** = Schizoaffective Disorder; **SCWT** = Stroop colour-word task; **SES** = socio-economic status; **SFG** = superior frontal gyrus; **SP** = schizophrenia patients; **STG** = superior temporal gyrus; **TL** = temporal lobe; **VF** = verbal fluency; **VR** = Visual Reproduction; **YOE** = years of education; **WAIS** = Wechsler Adult Intelligence Scale; **WBV**=whole brain volume; **WCST** = Wisconsin Card Sorting Task; **WM** = working memory; **WMS** = Wechsler Memory Scale; **WMV** = white matter volume.

Publication	Total subjects (M/F)	Cognitive measures	Structural Areas	Findings MRI deficits ↓ Reduction ↑ Increase	NP deficits	MRI/NP correlations MRI/NP = positive MRI/ - NP = negative
Szeszko et al., 2003	81 (48/33) FEP 23 (14/9) NC	**Executive, Motor, Language, Visuo-spatial, Mem, Attention,** and **Global** scales	**Cerebellum**	Not reported	Not reported	**NC:** Cerebellum/Global, Visuospatial, Executive, Mem scales **FEP:** none
Sanfilipo et al., 2002	62 (62/ 0) SP 27 (27/ 0) NC	Five factors: **Verbal IQ/endowment** (*WAIS-R:* Similarities, Vocabulary, DST, Information subtests; *WMS:* LM I and II); **CF** (M-WCST); **Word Mem** (BSRT); **Visual Mem** (*WMS:* VR, I and II); **VF** (Category Retrieval, COWA, ANT) + **DST** correlated with all factors	GMV and WMV: **PFC** **TL** **STG** **Hippo** **PHG**	↓ GMV: **PFC** **TL** **STG**	All factors, except **CF** Strongest effect for **VF**	**NC**: R Hippo/ VF, - Word Mem L & R PFC GMV/ DST **SP**: L & R Hippo/ Word Mem L & R PFC WMV/ CF R PHG (trend STG WMV)/ - Verbal IQ
Nestor et al., 2002	15 (15/ 0) SP	**WM**: Hebb's recurring digits, Trail Making A & B, Alternating Semantic Categories. **Verbal Mem**: Verbal paired associates, LM, I and II. **Categorisation**: WAIS-R Similarities, WCST categories completed	GMV: **PFC, STG**, posterior **TL, PHG** WMV: **PFC**	For MRI and NP deficits see Nestor et al. 1993		*First pair of latent variables*: L & R posterior STG, L & R PHG/ WCST, Similarities, Trail A, B and LM II *Second pair of latent variables*: L & R FL gray matter, L FL white matter/ Alternating Semantic Category, Hebb's RD, Trail B
Szeszko et al., 2002	75 (43/32) FES Schizophrenia and SAD=56	41 tests measuring six domains: **Memory, EF, Language, Attention, Visuo-spatial, MF**	**Hippo** anterior and posterior	-	-	**Men SP**: Anterior Hippo/ EF and MF, -> stronger than Mem and Language **Female SP**: none
Zuffante et al., 2001	23 (23/ 0) SP typical and atypical medication 23 (23/ 0) NC	**Full scale IQ**: WAIS-R **WM**: Spatial Delayed Response Task (SDRT); Self-Ordered Pointing, verbal and non-verbal	GMV and WMV: **BA 46**	No	Yes	**NC**: L BA 46/ - SDRT **SP**: none

Nopoulos et al., 2001	50 (50/ 0) SP (11 FEP) 50 (50/ 0) NC	**Full scale IQ**: WAIS-R	**Midbrain and cerebellar vermis** Pons and medulla as control regions	↓ **Midbrain** Vermis/midbrain correlation in SP but not in NC	Not reported	**NC**: none **SP**: none
Rossell et al., 2001	71 (71/0) SP: 41 with history of auditory verbal hallunications (AVH) and 21 without 31 (31/0) NC right- and left-handed	**Test of interhemispheric transfer:** Dichotic Listening Test **Laterality Test:** Finger Tapping	**CC** area and length; four sub-areas (mid-sagittal slice)	No	↓ Finger Tapping for both AVH and no AVH SP	**NC**: none **SP**: none
Szeszko et al., 2000	35 (20/15) SP	**Full scale IQ**: WAIS-R **Language, Mem, EF, MF, and Visuo-Spatial processing** scales	GMV and WMV: **SFG, Anterior Cingulate (AC) OFC**	-	-	**Male SP**: AC/ EF -> stronger than with other NP variables **Female SP**: none
Manschreck et al., 2000	16 (11/5) SP	**Motor synchrony**: a synchronized tapping response to rhythmic acoustic clicks *Two IVs*: interbeat interval score (IIS), synchrony accuracy (SA)	GMV and WMV: **WBV, DLPFC, DMPFC, OFC, corpus striatum, ventral pallidum, LV** (temporal horns)	-	-	FL and OFC/ - synchrony accuracy
Krabbenda m et al., 2000	27 (13/14) SP 19 (9/10) NC MRI sub-sample: 25 SP, 17 NC	SCWT, Concept Shifting Test (CST); Groningen Intelligence Test (GIT), three subtests	**TL, Amygdala /Anterior Hippo complex , PHG**	No	CST SCWT colour-word part	**NC**: none **SP**: L PHG/ - SCWT colour-word part
Gur et al., 2000a	70 (40/30) SP 29 neuroleptic naïve 41 previously treated 81 (34/47) NC	**Abstraction/Flexibility** **Attention** **Verbal Mem** **Spatial Mem** **Verbal Abilities** **Spatial Abilities**	GMV and WMV: **DLPFC** **DMPFC** **OFC** lateral and medial	↓ GMV: **DLPFC** in male bilaterally and in female on the right **DMPFC** in both genders **OFC lateral and medial** in women	Not reported	**NC men**: DLPFC/Abstraction and Attention DMPFC/Attention **NC women**: DLPFC, DMPFC/ Abstraction OFC lateral and medial/Spatial Mem OFC lateral/Spatial ability **SP men**: DMPFC/ Attention **SP women**: DLPFC/ Attention OFC medial /Verbal Mem
Gur et al., 2000 (b)	100 (58/42) SP 39 neuroleptic naïve 61 previously treated 110 (51/59) NC	**Abstraction-Flexibility** **Attention** **Verbal Mem** **Spatial Mem** **Verbal Abilities** **Spatial Abilities**	**Hippo** **Amygdala** GMV and WMV: **STG** **Temporal pole (TP)**	↓ GMV: **Hippo** and **TP** in both genders **STG** in men ↓ **Amygdala** in men ↑ **Amygdala** in women	Not reported	**NC men**: Hippo/ Verbal and Spatial Mem STG/attention **NC women**: Hippo and STG/ Spatial Mem TP/ Verbal and Spatial Mem, Abstraction and Spatial Abilities **SP men**: Hippo/ Verbal Mem **SP women**: Hippo/ Verbal and Spatial Mem
Nopoulos et al., 1999	65 (65/ 0) SP 65 (65/ 0) NC	**WAIS- R Full scale, Verbal and Performance IQ**	**Total cerebellum, cerebellar lobes, vermis:** anterior, superior posterior	↓ **Anterior vermis**	Not reported	**NC: none** **SP:** Anterior vermis/Full scale and Verbal IQ

			and inferior posterior			
Gur et al., 1999	130 (75/55) SP 51 neuroleptic naïve 130 (75/55) NC	**Abstraction/Flexibility** **Attention** **Verbal Memory** **Spatial Memory** **Verbal Abilities** **Spatial Abilities**	**GMV, WMV** (L and R hemisphere) and **CSF**	↓ **GMV** bilaterally with smaller volumes in female SP ↑ Ventricular **CSF**	All domains, with specific deficits in **Attention** and **Verbal Mem** No sex differences	**NC men**: GMV/Abstraction, Attention, Verbal and Spatial Abilities **NC women**: GMV/Verbal and Spatial Mem, Verbal Abilities **SP men**: GMV/Verbal and Spatial Mem and Abilities **SP women**: GMV/Attention, Verbal Mem, Verbal and Spatial Abilities
Levitt et al., 1999	15 (15/ 0) SP 15 (15/ 0) NC	Not specified	**Vermis**: lobules I-X. **Cerebellum**: total and L&R GMV and WMV	↑ WMV of **Vermis** ↑ L>R cerebellar asymmetry for GMV + WMV and GMV	-	**NC:** none **SP**: Vermis WMV/ - LM immediate
Baare et al., 1999	13 (13/ 0) SP 14 (14/ 0) NC	**Verbal and Visual Mem**: CVLT; VR of WMS **Subjective Ordering Tests:** digit span, missing item scan, randomization, sequential pointing **General verbal ability**: WAIS Comprehension and Vocabulary; VF	GMV and WMV: **PFC** **DLPFC** **DMPFC** **OFC**	No, but trend for smaller volumes	**Verbal and Visual Mem** **VF** **Sequential Pointing** **Comprehension**	**NC**: PFC/Verbal and Visual Mem, delayed **SP**: PFC/Verbal and Visual Mem, immediate
Zipursky et al., 1998	77 (43/34) FEP (S=46) 61 (34/27) NC	**NART** **Quick test**	Total **GMV** and **WMV** (excluding brainstem and cerebellum), **CSF**	↓ Total GMV Total CSF, ventricular CSF and trend for sulcal CSF	Not reported	**NC**: none **FEP**: Total GMV/ Quick test, trend for NART
Torres et al., 1997	20 SP: 10 (7/3) low and 10 (7/3) high on memory score 19 NC: 10(5/5) low and 9(4/5) high on memory score	Rey-Auditory Verbal Learning Test (RAVLT), LM I and II, Rey-osterreith Complex Figures Test (R-O), I and II	**WBV** and **TL** (semi -automated method) **Hippo** (manual tracing)	Not compared Significant R>L Hippo asymmetry in both low and high SP	-	**NC**: none **SP**: none
Stratta et al, 1997	35 (26/9) SP 24 (17/7) NC	**WCST**	Total **BG** **CN** **Putamen (Pu)** **Nucleus Accumbens (NA)**	*Poor SP performers:* ↓ L CN, Pu than controls ↓ R total striatum than controls ↓ L Pu, L&R Pu + Na than good SP performers *Good SP performers:* ↑ Pu , Pu + Na than controls (a trend)	Median split on WCST (4 categories completed): 12 good and 23 poor SP performers	**NC**: not reported **SP**: L striatum and Pu + Na complex/ WCST categories completed L Pu, Na, Pu+Na/ -WCST unique responses Separate correlations for good and poor performers were not reported

DeLisi et al., 1997a	41 FEP 26 NC NB: the sub-sample with NP assessment, gender not specified	**Receptive Language:** Goldman Fristoe Woodcock Test (GFWT), noise distraction and quiet conditions **Expressive Language:** BNT, COAT, Woodcock Reading Mastery Test, Oral soliloquy **Mixed:** Wide Range Achievement, WAIS-R; WMS **Nonverbal Ability:** Symbol Digit Modality Test (SDMT), Raven's Colored Progressive Matrices (RCPM), Vigilance Task **Hand Skill**: FT	L/R relative width of **anterior** and **posterior frontal, temporal** and **occipital** areas (axial slices) **Sylvian fissure (SF)**, anterior, horizontal and vertical segments (sagittal slices)	↓ Temporal and occipital L>R asymmetry ↓ L horizontal segment of SF at a trend level ↓ L>R asymmetry of the horizontal segment of SF (trend) ↓ Normal male>female asymmetry of the anterior frontal area	RCPM, SDMT, COAT,GFWT (noise distraction and quiet conditions), LM I VR I and II, Vigilance Task, Oral Soliloquy (more morphological errors and less clausal embedding)	**NC:** L>R horizontal SF asymmetry/ GFWT noise distraction, - GFWT quiet condition, Nonverbal Ability R>L posterior frontal and anterior SF asymmetry/ - COAT R>L anterior frontal, L>R temporal asymmetry/ Verbal Mem R>L anterior frontal asymmetry/ Nonverbal Ability **SP:** L>R occipital asymmetry/ - Sentence complexity R>L anterior SF, L>R horizontal SF asymmetry/ Vigilance -> Non-significant with Bonferroni correction
Woodruff et al., 1997a	Sub-sample: 27 (27/0) SP 29 (29/0) NC	**Test of interhemispheric transfer:** Modified Stroop task (bilateral facilitation and interference indices)	**CC** total area and 4 segments (mid-sagital slice).	No	Less interference	**NC:** none **SP:** CC posterior/ - Bilateral interference, Bilateral facilitation (trends)
Sullivan et al., 1996	34 (34/ 0) SP 47 (47/ 0) NC	**IQ:** NART, Vocabulary WAIS-R **EF**: verbal and non-verbal self-ordered pointing, nonverbal temporal order discrimination, verbal and nonverbal visual search, WCST **Short-Term Mem and Production:** verbal and nonverbal Brown-Peterson distracter tasks, letter and design fluency **Motor Ability:** grip strength and fine finger movements **Declarative Memory:** WMS	Total **GMV, WMV** and **CSF, prefrontal, frontal, frontal-temporal, temporal-parietal, parietal** and **parietal-occipital regions** (semi-automated segmentation)	↓ Total cortical **GMV**	**NART** and **Vocabulary IQ** All four cognitive domains	**NC:** none **SP**: GMV/all four cognitive domains, but not NART or Vocabulary Age Scaled Scores
Bilder et al., 1995	29 (18/11): SP = 24 SAD =5	**Full scale IQ**: WAIS-R **Language, Mem, Attention, EF, MF** **Visuo-Spatial Abilities**	**Amygdaloid complex** **Hippo** anterior and posterior	-	-	Anterior Hippo/ EF, stronger than FSIQ Anterior Hippo/MF
Maher et al., 1995	18 (13/5) SP	**Short-term Mem**: 4 lists of words in increasing order of approximation to English sentences: lists 1 & 2 = context free; lists 3 & 4 = context aided	**WBV, FL, DLPFC, DMPFC, OFC, Striatum, ventral pallidum, LV**	-	Context-free worse than context-aided recall	FL/context-aided DLPFC/context-aided Striatum/ - context-aided

Vita et al., 1995	19 (12/7) SP 15 (9/6) NC	**NP:** VF, Picture Naming test (PNT), Sentence Generation Test (SGT)	(temporal horns) GMV and WMV: **PFL, TL, STG,** **LV:** frontal, body, temporal, occipital	↑ LV: body segment bilaterally and right occipital horn		STG/ VF semantic L TL and STG/ - PNT number of errors LV/ - SGT
Kareken et al., 1995	68 (43/25) SP Deficit sub-type = 22 68 (43/25) NC	**Abstraction/Mental Flexibility (AMF)**: WCST **Attention**: CPT, SCWT, Trail A&B **Verbal Mem**: LM, CVLT **Visuo-Spatial Mem (VSM)**: Design Reproduction of WMS **Language**: COWA, ANT, BNT, Token Test **Visuo-Spatial Perception (VSP)**: Block Design, Benton Line Orientation, Geometric Figure Drawing **Sensory**: Double Simultaneous Sensory Stimulation, Graphesthesis **Motor**: FT, Thumb-Finger Sequential Touch	**WBV** Ventricular **CSF Ventricle to Brain Ration (VBR)** (excluding 3rd V due to low inter-rater reliability) Semi-automated tissue segmentation	↑ VBR *Deficit SP:* ↓ WBV relative to controls	All domains Greatest impairment on **Verbal Mem** *Deficit SP:* Greater cognitive impairment overall, but the same pattern as in non-deficit SP	**NC**: VBR/ - VSP, - AMF WBV/ Attention, AMF, VSM, Language, VSP Ventricular CSF/ - VSP **SP**: WBV/ AMF, Verbal Mem, Language **Deficit SP:** WBV/ AMF, VSM, Language **Non-deficit SP:** WBV/Language
Goldberg et al., 1994	15 (8/7) pairs of monozygotic twins discordant for schizophrenia	**Full scale IQ**: WAIS-R **Memory**: *WMS*: LM, VR, Paired Associates **Psychomotor speed:** Trail A **Automatic lexical access:** Stroop color reading **EF**: WCST **Verbal ability**: VF phonological **Attention**: CPT (self-paced version)	**Hippo, 3rd ventricle, section of LV** (coinciding with the longitudinal axis of the TL)	↓ All three areas as found in the previous analysis	All domains	*Volume indexes/ performance ratios (IQ adjusted):* L Hippo, PFC/LM L&R Hippo, PFC/Psychomotor speed
Seidman et al., 1994	17 (14/3) SP 13 right-handed	**Frontal function**: WCST, categories and perseverative responses; Similarities of WAIS –R, CPT; FT **TL tests**: WMS-R: LM I and II; VR **IQ**: WAIS-R, vocabulary and block design	**WBV** **FL** **DLPFC** **OFC** **TL** (semi-automated method)	-	-	L LV / - WCST perseverative errors WBV/Similarities Total DLPFC/ IQ, WCST categories, - WCST perseveration, LM II L DLPFC/IQ, WCST categories, -WCST perseveration, LM I and II, Similarities,VRI R DLPFC/ - CPT error -> contrasted against TL -> DLPFC / WCST, IQ, WAIS-R Similarities at trend level L DLPFC/Similarities - the strongest trend
Flaum et al., 1994	72 (50/22) SP 59 (32/27) NC	**Full Scale IQ**: WAIS-R	**WBV** **TL** **LV** **Hippo** **CN** **Pu** **Cerebellum**	Not compared	Yes	**NC**:FSIQ/L&R WBV, L & R TL, L Hippo and cerebellum -> FSIQ/R TL significantly stronger, trends for L TL and L&R cerebrum **SP**: none **SP women**: FSIQ/ L TL, L & R Hippo, cerebellum, and L Pu, trends for cranium and cerebrum **SP men**: none
Hoff et al., 1994	48 (35/13) FEP 22 (12/10) NC	**Language**: e.g. Pro-rated verbal IQ, BNT **EF**: WCST, categories completed and perseverative responses, SCWT **Verbal Mem**: CVLT, LM I and II **Spatial Mem**: BVRT, VR **Concentration/Speed**: Trail A&B, Symbol Digit Modalities Test, FT **Sensory/Perceptual**: Finger Gnosis, Finger	**CC total area** (single most medial slice)	↓ CC in SP women than NC women or SP men	Yes	**NC:** CC/EF, Verbal Mem, Concentration/Speed, Sensory/Perceptual, Global, Right Hemisphere **SP:** none

		Number Writing **Global:** mean of all sub-scales **Right Hemisphere:** e.g. BVRT, VR, FT left, Finger Gnosis left **Left Hemisphere:** e.g. verbal IQ, LM, Associate Learning, CVLT, FT right, Finger gnosis right NB: only the most common tests listed				
Nestor et al., 1993	15 (15/ 0) SP	**Abstraction and categorization**: Similarities WAIS-R, WCST categories completed **Learning and Mem:** *WMS-R*: LM I and II, VR, Verbal paired associates learning **Control tasks**: FT, Block design of WAIS-R	**TL** **STG** anterior and posterior **PHG** **Hippo**	-	**Similarities, LM, Block design** -> the low end of the normal range ↓ **WCST**	L & R PHG, L & R posterior STG/ WCST, Similarities L posterior STG/Verbal paired associates Control tasks -> no correlations
Colombo et al., 1993	18 (12/6) SP 18 (13/5) NC.	**Mem**: WMS, 7 subtests Three factors: I= immediate learning and recall abilities II = attention and concentration III= orientation and long-term information recall	**WBV, Lateral** (temporal horns) and **3rd ventricles, L and R TL, L and R Hippo**	No	Yes	No correlations performed
Hoff et al., 1992	56 (41/15) FEP left handed = 7 57 (39/18) NC left handed=9 *MRI sample*: 37 FEP 21 NC Some FEP were on lithium in addition to haloperidol 17 FEP had NP follow up data	**Language**: e.g. Pro-rated verbal IQ, BNT **EF**: WCST, categories completed and perseverative responses, SCWT **Verbal Mem**: CVLT, LM I and II **Spatial Mem**: BVRT, VR **Concentration/Speed**: Trail A&B, Symbol Digit Modalities Test, FT **Sensory/Perceptual**: Finger Gnosis, Finger Number Writing NB: only the most common tests listed	**WBV** **LV** **TL** **limbic complex** (Amygdala + Hippo +PHG) **Lateral Sulcus (LS)** bordering the superior portion of Planum Temporale	**SP women**: abnormal LS L/R ratio (L LS smaller than in other groups, right LS similar to others) For other regions see DeLisi, 1991	All scales *Follow up*: significant improvement on **EF, Conc/Speed**, and trend for **Sensory/Perceptual**	**NC**: L LV/ - Cons/Speed, - Sensory/Perceptual R LV/ - EF, - VerbMem, -Sensory/Perceptual, - Left Hemisphere scale, - Global scale LS L/R ration / - Sensory/Perceptual, - R Hemisphere scale **SP**: R TL/ Concentration /Speed R limbic complex/Language R LS/Spatial Mem, Concentration/Speed, Right Hemisphere scale, Global scale LS L/R ration/ -VerbMem *Normal vs. abnormal laterality SP sub- groups:* abnormal -> better Verbal and Spatial Mem, EF and Global scale than normal (No differences in NC)
Bornstein et al., 1992	72 (49/23) SP 31 (13/18) NC	**WAIS-R** **WMS-R** **WCST** **Verbal Concept Formation Test** (VCAT) **Halstead-Reitan Neuropsychological Battery**	Ventricle to brain rations (VBR): **LV, 3rd Ventricle**	↑ 3rdV VBR **Male SP**: None **Female SP**: ↑ LV VBR	Not reported	**NC**: 3rdV VBR/ IQ, VF LV VBR/Verbal IQ **SP including SAD:** LV VBR/Verbal IQ, - Visual span, - FT 3rd V VBT/ - Verbal IQ, - VCAT, - WCST categories, WCST perseveration, - Seashore Rhythm, - Visual span, - Digit Span, Trail Making A, - Knox cube delayed **SP excluding SAD**: LV VBR/ - Visual span, FT 3rd V VBR/ -VCAT, -WCST categories, -Seashore rhythm, -Digit Span
Di Michele et al., 1992	25 (13/12) SP 17 (10/7) NC	Luria-Nebraska battery: **Motor, Rhythmic, Tactile, Visual, Receptive speech, Expressive speech, Writing, Reading, Arithmetic, Memory, Intelligence**	**L and R TL**	*Overall*: ↓ **L & R TL**, L<R (NC: no difference between L and R TL)	Abnormal more impaired than normal on **Motor, Rhythmic,**	**NC:** none **SP:** none

Raine et al., 1992	17 (10/7) SP 18 Psychiatric controls (PC) (12/6) 19 NC (10/9) MRI data sub-sample not specified	SP were divided into *normal* (14) and *abnormal* (10) groups based on the total score **FL measures**: WCST categories completed and perseverative errors, Spatial Delayed Response Task (SDRT), Block Design Test **Non-frontal measures**: verbal dichotic listening, nonverbal dichotic listening, and finger sequence repetition (FSR)	**L** and **R PF** area s (coronal, midsaggital, transverse cuts) **Posterior** area (midsaggital cut) **L** and **R posterior** areas (transverse cut) **L** and **R TL** areas (coronal cut)	*Abnormal SP*: ↓ **L & R TL**, L>R ↓ **L PF** coronal area relative to both control groups ↓ **R PF** coronal area relative to PC ↓ **L & R PF** midsaggital areas relative to PC ↓ **L & R PF** transverse areas relative to both groups	**Visual, Receptive speech, Mem, IQ SDRT** and **WCST** perseveration relative to NC **Block Design** relative to both groups No significant differences for **non-frontal tasks**	No correlations performed
DeLisi et al., 1991a	30 (23/7) FEP 15 (9/6) SP 20 (12/8) neurological controls (NeuroC)	**Premorbid IQ**: Reading subtest of Wide Range Achievement Test **Verbal IQ**: information, vocabulary and similarities sub-tests of WAIS-R **Cognitive measures**: *WMS*: LM I and II, Associate Learning (two short-term verbal memory forms) and VR; CVLT; Benton Visual Retention Test (BVRT); WCST; Booklet Categories Test; BNT; VF; Trail Making B	*Coronal slices:* **WBV, FL, TL, Amygdala/Hippo complex, PHG, LV, Temporal and Frontal ventricular horns** *Axial slices:* **CN, LN** (GP+Pu)	*FEP:* ↑ **L LV** than NeuroC ↑ **R LV** than NeuroC at trend level ↑ **Bilateral Frontal horn** than NC *SP:* ↑ **L LV** than FEP	Not reported	**NeuroC:** not reported **FEP + SP**: Bilateral Hippo/Associated Learning Bilateral PHG/Verbal IQ **FEP:** Bilateral Hippo/Associated Learning Bilateral PHG/LM
Raine et al., 1990	15 (9/6) SP 13 (9/4) PC 18 (9/9) NC	**Tests of Interhemispheric Transfer:** Verbal Dichotic Listening Nonverbal Dichotic Listening Finger Sequence Repetition Tactile Intermanual Task Block Design	**CC:** area, length, anterior, middle, and posterior thickness	↑ **CC** anterior thickness in SP women relative to NC men	No	No correlations performed

TABLE 2.2. Reviewed studies clustered by structure

Whole Brain Volume	Flaum et al., 1994; Gur et al., 1999; Karenken et al., 1995; Maher et al., 1995; Seidman et al., 1994; Torres et al., 1997; Zipursky et al., 1998
LV & 3rd V	Bornstein et al., 1992; DeLisi et al., 1991a; Hoff et al., 1992; Goldberg et al., 1994; Maher et al., 1995; Vita et al., 1995
PFC	Baare et al., 1999; DeLisi et al., 1991a; Gur et al., 2000 (a); Maher et al., 1995; Manschreck et al., 2000; Nestor et al., 2002; Raine et al., 1992; Sanfilipo et al., 2002; Seidman et al., 1994; Sullivan et al., 1996; Vita et al., 1995; Zuffante et al., 2001
TL	DeLisi et al., 1991a; Di Michele et al., 1992; Flaum et al., 1994; Gur et al., 2000 (b); Hoff et al., 1992; Jeste et al., 1998; Krabbendam et al., 2000; Maher et al., 1995; Nestor et al., 1993, 2002; Raine et al, 1992; Sanfilipo et al., 2002; Seidman et al., 1994; Sullivan et al, 1996; Torres et al., 1997; Vita et al., 1995
STG	Gur et al., 2000 (b); Nestor et al., 1993, 2002; Sanfilipo et al., 2002; Vita et al., 1995
Hippocampus/Amygdala	Bilder et al., 1995; DeLisi et al., 1991a; Di Michele et al, 1992; Flaum et al., 1994, Goldberg et al., 1994; ; Gur et al., 2000 (b); Hoff et al., 1992; Krabbendam et al., 2000; Nestor et al, 1993; Sanfilipo et al., 2002; Szeszko et al.,2000, 2002; Torres et al., 1997
PHG	DeLisi et al., 1991a; Di Michele et al., 1992; Hoff et al., 1992; Krabbendam et al., 2000; Nestor et al., 1993, 2002; Sanfilipo et al., 2002
Parietal, Parieto/occipital	Raine et al., 1992; Sullivan et al., 1996
Basal Ganglia	DeLisi et al., 1991a; Flaum et al., 1994; Jeste et al., 1998; Levitt et al., 1999; Maher et al., 1995; Manschreck et al., 2000; Stratta et al., 1997
Thalamus	Jeste et al., 1998
Midbrain	Nopoulos et al., 2001
Cerebellum	Levitt et al., 1999; Nopoulos et al., 2001
Corpus Callosum	Raine et al., 1990; Hoff et al., 1994; Woodruff et al., 1997a; Rossell et al., 2000
Brain asymmetry	Hoff et al., 1992; DeLisi et al., 1997a

2.5.1. Whole brain volume

2.5.1.1. Introduction

Whole brain volume reduction in patients with schizophrenia is found in only 22% of the studies (Shenton et al., 2001). Studies that have carefully matched patients and normal controls on parental educational levels have failed to find reduced brain volumes in patients (DeMyer et al., 1988; Andreasen et al., 1990; Pearlson et al., 1991). One study has observed an excess of both smaller and larger head size, suggestive of dysmorphic crania in schizophrenia patients rather than a systematic decrease in head or brain size (Green et al., 1989). Thus, the notion of reduced brain size in schizophrenia remains controversial.

There is a relationship between brain size and general intelligence in normal subject that goes beyond the differences in body and head size (Van Valen, 1974). The correlation of 0.38 between brain size and full scale IQ as measured by Wechsler Adult Intelligence Scale (WAIS-R, Wechsler, 1981) was found in healthy normal control subjects (Andreasen et al., 1993). It is not clear whether this relationship between brain size and general intelligence is present in schizophrenia.

2.5.1.2. Relationship of whole brain volume to cognition

Eight studies have investigated the relationship between the whole brain volume (WBV) and cognitive function, six studies with a control group (Colombo et al., 1993; Flaum et al., 1994; Kareken et al., 1995; Torres et al., 1997; Zipursky et al., 1998; Gur et al., 1999), and two without (Seidman et al., 1994; Maher et al., 1995). Of those six studies with a control group, two studies (Flaum et al., 1994; Torres et al., 1997) did not compare patients and controls on the WBV.

Two studies that compared patients and controls matched on parental socio-economic status found reduced whole brain grey matter volume in first-episode (FE) patients (Zipursky et al., 1998) and chronic patients, particularly women with schizophrenia (Gur et al., 1999). White matter volume was found to be unchanged in both studies. The third study (Colombo et al., 1993) that compared patients and controls on WBV did not segment the brain tissue into grey and white matter compartments and observed no WBV alterations in schizophrenia patients. Thus, alterations in overall brain tissue availability in schizophrenia might be limited to grey matter. Alternatively, reduction in WBV might be limited to a specific sub-group of schizophrenia patients, as found by Kareken et al.

(1995), who reported WBV reduction in deficit, but not in non-deficit, patients relative to normal controls.

Almost all measures of cognitive functioning were found to correlate with the WBV, and particularly total grey matter, indicating 'bigger brain-better performance' relationship in controls as well as in patients, with the most reliable associations found for the measures of general intellectual ability and composite cognitive processes such as language, abstraction/flexibility, and verbal and spatial reasoning (Seidman et al., 1994; Kareken et al., 1995; Gur et al., 1999). The relationship between WBV and memory was not as consistent, with Gur and colleagues (1999) reporting a positive association in both patients and controls, whereas other studies finding no relationship of immediate and delayed memory to WBV either in patients (Colombo et al., 1993; Maher et al., 1995; Torres et al., 1997) or in controls (Torres et al., 1997).

There were findings for both patients and normal controls that did not fit into 'bigger brain-better performance' pattern. Firstly, Flaum and colleagues (1994) found a normal relationship between WBV/IQ in female, but not in male, patients. Secondly, healthy controls failed to show a WBV/IQ association, when such a relationship existed in first episode (FE) patients of mixed gender, with a significant difference in the strength of grey matter/IQ correlations between the groups (Zipursky et al., 1998). And finally, there were points of convergence and divergence in the WBV/cognition relationship amongst the predominantly male controls, deficit and non-deficit patients (Kareken et al., 1995), such that significant positive correlations existed between WBV and i) language for all groups; ii) abstraction/mental flexibility for controls and deficit patients; iii) attention, visuo-spatial memory and visuo-spatial perception for controls only; and iv) verbal memory for deficit patients only.

Summary: WBV has a non-specific relationship with cognition, associating with the level of general intelligence as well as with more specific cognitive abilities in both patients and controls. The magnitude of WVB/IQ association in patients appears to be reflecting a normative relationship ($r = 0.39$, Seidman et al., 1994). However, some of the findings point towards a more complex, and, perhaps, non-linear relationship between brain size and cognitive abilities in male patients.

2.5.2. Ventricular size

2.5.2.1. Introduction

Enlargement of lateral ventricles (LV) is found in 80% of the studies, while the third ventricle is found to be enlarged in 73% of the studies (Shenton et al., 2001). Ventricular enlargement is present at the onset of the illness and is associated with poor premorbid adjustment (Weinberger et al., 1980; DeLisi et al., 1983), more severe negative symptoms (Andreasen et al., 1982; Pearlson et al., 1984; Kemali et al., 1985), and is generally predictive of poor outcome in schizophrenia (DeLisi et al., 1983).

The enlargements of the LV and of the third ventricular cavity might indicate morphometric abnormalities in the structures of the temporo-limbic complex and thalamus that are part of cortico-temporo-limbic-cortical and cortico-striato-thalamo-cortical circuits respectively. Consequently, the enlargement of the ventricles might be associated with disrupted performance on tests of higher cognitive functions that are subserved by these circuits. These might include verbal learning and memory as well as attention and concentration.

2.5.2.2. Relationship of ventricular size to cognition

Six studies have investigated the relationship between the ventricular size and cognitive deficits, four with a comparison group (Bornstein et al., 1992; Hoff et al., 1992; Goldberg et al., 1994) or groups (DeLisi et al., 1991a), and two without (Maher et al., 1995; Vita et al., 1995).

Two studies did not find any associations between an absolute size of lateral ventricles (LV) and cognitive performance in patients (DeLisi et al., 1991a; Hoff et al., 1992), despite the increased LV size in FE and chronic patients relative to neurological controls, with greater prominence on the left side in the DeLisi et al. study. The latter study has also measured the size of the third ventricle, finding no size differences or relationship with cognitive function. In the study by Hoff et al. (1992), almost all cognitive domains inversely correlated with LV size in normal controls, with smaller left LV being associated with better concentration/speed and sensory/perception, and smaller right LV being associated with better executive function, concentration/speed, sensory/perception, a global performance scale, verbal memory and a left hemisphere scale. (The association of right LV size with the left hemisphere scale might be due to the mixed handedness sample.) When a sub-sample of patients was reassessed on neuropsychological measures 2 years later, there was

significant improvement on the domains that were most impaired at the time of the initial assessment, that is, executive function, concentration/speed, global scale, and, at the trend level, sensory/perceptual scale. Noteworthy, these are the scales that were found to correlate with the LV size in normal controls. It is possible that the severity of cognitive impairment was partly related to symptomatic state at the time of the first assessment in this sample of FE patients. However, the relationship between symptoms rating and cognitive function was not reported. The possibility that the pattern of correlations similar to that of controls between cognitive scores and LV size would have been found in these patients at 2-year follow-up is intriguing; however, there are no data available on follow-up relationship between cognitive and LV measures.

A counter-intuitive relationship of enlarged absolute LV size and less perseveration has been found in the study of 15 pairs of monozygotic twins discordant for schizophrenia (Goldberg et al., 1994). Affected twins also showed an enlargement of the LV temporal horn and of the third ventricle, but these did not associate with cognitive deficits. Another study (Vita et al., 1995) measured the segments of LV, including frontal, body, temporal, and occipital, in chronic patients and found a significant enlargement of the LV body, but this was unrelated to language function.

The absence of correlations between the ventricular size and cognitive deficits in schizophrenia patients in the studies reviewed might be due to the use of absolute volume measurements. Since patients with schizophrenia might have smaller as well as larger than average cerebrums (Green et al., 1989), relative measurements of ventricular size might be more appropriate. Indeed, a study (Bornstein et al., 1992) that calculated ventricle to brain ratio (VBR) has found enlarged lateral VBR to associate with worse forward Visual Span (attention/concentration), as well as finger tapping task using the non-dominant hand (psychomotor speed) in female schizophrenia patients. However, these associations were attenuated in affected men. Third VBR was also enlarged in men and women with schizophrenia relative to healthy counterparts, and inversely correlated with the tests of abstraction/categorization (Verbal Concept Formation Test, WCST categories completed) and attention/concentration (Seashore Rhythm, Digit Span). Surprisingly, in normal controls, larger lateral VBR and third VBR were associated with better cognitive performance, including larger lateral VBR with verbal IQ; and third VBR with verbal fluency and verbal concept formation. These positive correlations in controls are difficult to interpret. Fewer correlations between VBR and cognitive measures in controls

overall might be due to almost negligible variability in VBR, presumably due to the linear relationship between ventricular and brain sizes. In patients, on the other hand, the mean values for the third VBR were twice the magnitude of those found in controls with substantial variability, indicating disproportionately larger third ventricle in relation to brain size on average. In the final study employing VBR measurements (Maher et al., 1995, see also *Whole brain volume*), which examined neural correlates of short-term memory in schizophrenia, neither absolute nor relative LV size correlated with context-free or context-aided free recall.

Summary: Four main points emerge regarding the relationship of ventricular size to cognition: (1) the relationship between ventricular size and cognitive function is complex, with both larger LV (in normal controls and female patients; Hoff et al., 1992) and smaller LV (in controls; Bornstein et al., 1992; and in male patients; Goldberg et al., 1994) being associated with better cognitive functioning; (2) the relationship between LV size and cognitive functioning might be disrupted in affected men (Hoff et al., 1992), paralleling the findings observed for WBV and IQ; (3) the abnormality of ventricular size and its association with cognitive measures are more reliably found when the measures of relative, as opposed to absolute, size are used; and (4) the size of the third ventricle might be more illuminating as to the nature of the cognitive disturbances in schizophrenia, as third ventricular enlargement might indicate the pathology of the thalamus, which is immediately adjacent to the third ventricle. This putative thalamic abnormality might cause disruption of cortico-striatal-thalamo-cortical as well as cortico-cerebellar-thalamo-cortical circuitry, resulting in deficient abstraction/flexibility and attention/concentration (Bornstein et al., 1992).

2.5.3. Frontal lobe

2.5.3.1. Introduction

Only 60 % of the studies reported abnormality of the frontal lobe in schizophrenia patients (Shenton et al., 2001). However, the frontal lobe is a large area, comprising 30 % of human cerebral cortex and consisting of highly differentiated (both cytoarchitectonically and functionally) regions. Studies that examined subregions of frontal lobe, such as dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC) and orbito-frontal cortex (ORFC) have consistently noted abnormalities in DLPFC structure (Shenton et al., 2001). However, the differences found are small.

As prefrontal cortex sends efferents and receives afferents from all other cortical and almost all subcortical brain regions (Fuster, 1980), the dysfunction of prefrontal cortex and cognitive processes associated with it may potentially arise due to the abnormal structure and/or function of any region it connects with. There is a growing awareness that impaired performance on frontal lobe tasks in schizophrenia might result due to an abnormality of subcortical structures such as striatum (Robbins, 1990; Stratta et al., 1997) or limbic cortex (Weinberger, 1987; Szeszko et al., 2002). Therefore, in this section, it is of particular interest if frontal lobe functions are associated with the structural alterations of PFC.

The studies that examined the whole frontal lobe (FL) are reviewed first, followed by the studies that parcellated prefrontal lobe into sub-regions.

2.5.3.2. Whole FL

Seven studies have investigated neuropsychological correlates of total FL volume, six with a control group (DeLisi et al., 1991a; Vita et al., 1995; Sullivan et al., 1996; Baare et al., 1999; Sanfilipo et al., 2002) or groups (Raine et al., 1992), and one without (Nestor et al., 2002).

Only two of these studies found reduced FL volume in patients relative to normal (Raine et al., 1992; Sanfilipo et al., 2002) and psychiatric (Raine et al., 1992) controls, which might be limited to grey matter (Sanfilipo et al., 2002). Baare et al (1999) observed smaller GMV and WMV in patients, but had low power to detect significance.

Two studies with a control group observed differences in structure/function relationships for patients and controls. Sanfilipo and colleagues (2002) found greater prefrontal GMV to be associated with better performance on Digit Symbol task in controls, but not in patients. On the other hand, a positive relationship existed between prefrontal WMV and cognitive flexibility in patients, but not in normal controls. In the second study (Baare et al., 1999), relative PFC volume was associated with verbal fluency and immediate recall for verbal and visual material in patients, and with delayed recall for visual stimuli in controls. These differences in associations between patients and controls might be due to the relative difficulty of the tasks. As suggested by the authors, delayed visual recall, being a more demanding task, could produce more variability in controls, and thus correlate stronger with PFC volume. By the same token, in patients, this task might produce a 'floor' effect and hence low variability, resulting in a weak correlation with PFC volume.

Two studies without a control group have reported a relationship between FL volumes and the performance on the so-called frontal lobe tasks. Nestor and colleagues (2002), using partial least square analysis, found an association between greater GMV and WMV and better working memory in patients. Raine and colleagues (1992) investigated a sub-group of patients with an impaired performance on frontal, but not non-frontal, measures, and found bilateral PFC reductions when compared with normal and psychiatric (predominantly major depressive disorder) controls (Raine et al., 1992).

Other studies did not find any relationship between prefrontal volumes and cognitive abilities in patients, perhaps due to an approximate definition and measurement of the ROIs corresponding to anatomical brain regions and an arbitrary construction of cognitive domains (Sullivan et al., 1996), as well as a lack of grey and white matter segmentation in two early studies (DeLisi et al., 1991a; Raine et al., 1992).

Summary: Total FL volume is associated with executive functioning, working memory, verbal fluency, and immediate memory in schizophrenia. There were differences in the pattern of structure/function relationship between patients and controls, which might be due to different degrees of variability in performance depending on the relative difficulty of the task (Baare et al., 1999), as well as the volumes of prefrontal brain tissue, with patients being more variable in prefrontal WMV, and controls being more variable in prefrontal GMV (Sanfilipo et al., 2002). Additionally, similar volumes of prefrontal grey matter in schizophrenia may not result in similar levels of cognitive performance to that of controls; for example, due to disrupted connectivity between PFC and other regions involved in the cognitive processes engaged by the task, or due to the lack of strategy use, prohibiting an optimal utilization of available prefrontal grey tissue.

2.5.5.3. Regions of PFC

Seven studies have examined neuropsychological correlates of the PFC sub-regions: four (Maher et al., 1995; Baare et al., 1999; Manschreck et al., 2000; Gur et al., 2000a) studied dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and orbito-frontal cortex (OFC); one (Seidman et al., 1994) investigated DLPFC and OFC; one (Szeszko et al., 2000) examined the superior frontal gyrus, anterior cingulate and OFC; and one (Zuffante et al., 2001) focused on Brodmann area 46. All, but three studies (Seidman et al., 1994; Maher et al., 1995; Manschreck et al., 2000) had a control group.

Of the two studies with a control group exploring DLPFC, DMPFC, and OFC, one study (Gur et al., 2000a) observed alterations in all three sub-regions. Gur and colleagues (2000a) reported a reduction in DLPFC volume in both male and female patients, a greater DMPFC volume reduction in males than females, and OFC reduction only in females. These reductions were limited to grey matter. The GMVs of the sub-regions were examined in relation to six cognitive domains (abstraction/flexibility, attention, verbal and spatial memory, and verbal and spatial abilities), predicting correlations with abstraction/flexibility and attention. Correlations with other domains were exploratory and were adjusted for multiple comparisons ($p < .01$). In accordance with the prediction, greater GMV of DLPFC correlated with better performance on abstraction/flexibility, and greater GMV of DLPFC and DMPFC correlated with better attention in healthy men. For healthy women, greater GMV of DLPFC and DMPFC correlated with better abstraction/flexibility. For male patients, correlations between the GMV of DLPFC and cognitive domains of interest were attenuated, and the only positive correlation was found between DMPFC and attention. For female patients, greater GMV of DLPFC was associated with better attention; greater GMV of lateral and medial OFC with better spatial memory; greater GMV of lateral OFC with spatial abilities; and greater GMV of medial OFC with better verbal memory. These findings are in line with functional and lesion data, which suggests that dorsal PFC is associated with executive function, while ventral PFC is involved in memory (Miller and Cohen, 2001).

In another study (Maher et al., 1995; see *Ventricular size*), contextual memory, but not rote memory, correlated positively with the relative frontal volume in schizophrenia patients (mostly male), with the main contribution of DLPFC to this relationship. According to the authors, this finding suggests the DLPFC is associated with redundancy utilization during verbal memory tasks, presumably by facilitating the encoding of information through the use of context.

In a later study from the same laboratory (Manschreck et al., 2000), the authors tested the hypothesis that motor synchrony, a task requiring redundancy utilization for optimal performance, would be associated with PFC volume and with context-aided verbal memory in a group of predominantly male patients with schizophrenia or schizoaffective disorder. Greater volumes of OFC were found to associate with poor motor synchrony. As suggested by the authors, this result might be artifactual in a sense that greater OFC volume might simply reflect smaller volume of DLPFC, which was positively correlated with context-aided

memory in the earlier study (Maher et al., 1995). However, this does not explain why neither absolute nor relative DLPFC volumes were found to correlate with motor synchrony in Manschreck's et al. study. Alternatively, the authors further commented, this association might reflect the role that OFC plays in organizing repetitive behavior. This, however, does not explain why larger OFC volume would be associated with poorer motor synchrony. A possible interpretation of this association might be related to the fact that OFC, by the virtue of its connections with limbic and olfactory cortices, plays a role in affective processing. Larger volumes of OFC might result in heightened affective salience of the stimuli in individuals with schizophrenia - a feature of cognitive processing that would be detrimental for utilization of redundancies in the stream of stimuli. In fact, one of the phenomenological features of schizophrenic experience is that every event is perceived as salient or meaningful (Hemsley, 1994). However, as no normal control group has been used in the study, it is not known whether OFC volumes were in fact enlarged in this patient group.

Seidman and colleagues (1994) examined the relationship of DLPFC and OFC volumes with verbal and performance IQ, verbal and spatial memory, and executive function in a predominantly male group of chronic schizophrenia inpatients. Greater total DLPFC volume was associated with higher IQ, as well as better performance on WCST and delayed Logical Memory. Hemisphere specific associations were also found, such that greater left DLPFC volume was associated with higher IQ, better WCST, Similarities, immediate and delayed Logical Memory, and immediate Visual Reproduction performance, whereas greater right DLPFC was associated with fewer errors on the Continuous Performance Task (CPT). OFC did not correlate significantly with any neuropsychological measures.

Szeszko et al. (2000) measured grey and white volumes of superior frontal gyrus (SFG), anterior cingulate (AC), and OFC in order to test the hypothesis that the dorsal 'archicortical' (SFG and AC), but not ventral 'paleocortical' (OFC), PFC would be associated specifically with executive and motor function in FEP patients. Tests of language, attention, memory, and visuo-spatial function were used as control variables to examine the specificity of findings. Their hypothesis was confirmed in male, but not in female, patients: larger AC volume correlated with better executive function, and this association was significantly stronger than with other cognitive domains and general IQ. This finding is in agreement with the results of Seidman et al. (1994) study (reviewed above), in which archicortical, but not paleocortical, PFC volume associated with executive function

in a cohort of predominantly male patients. However, the part of the archicortex associated with executive function was different in two studies, which might be due to different methodology, with Szeszko and colleagues (2000) using gyral landmarks for measuring the volume of the sub-region, whereas Seidman and colleagues (1994) calculated volume from a single slice. The difference might also be due to the tests employed, with Szezsko and colleagues using the measures of executive and inhibitory motor control, which are associated with AC function (Braver et al., 2001), while Seidman and colleagues used the measures of abstraction/flexibility, categorization and sustained attention, which are most robustly associated with DLPFC function (Garavan et al., 2002). Nevertheless, both studies have found an involvement of the archicortex in executive cognitive and motor function, but not of the paleocortex, which is associated with guiding emotional aspects of cognition (Fuster, 1980).

The last study (Zuffante et al., 2001) to be reviewed here tested a very specific hypothesis. The authors measured Brodmann area (BA) 46 and working memory in 23 male schizophrenia patients and 23 male healthy controls to investigate whether compromised working memory in schizophrenia is associated with BA 46 volume, an area known to be associated with working memory function in primates (Goldman-Rakic, 1987) and healthy humans (McCarthy et al., 1994). The patients did not show BA 46 volume alterations, but had impaired performance on spatial and non-spatial working memory tasks, which was not independent of lower general intelligence. There was no association between working memory performance and BA 46 volume in patients. These findings might imply that working memory impairment could arise due to several possibilities, including: i) structural abnormalities in other PFC regions supporting working memory, such as BA 9 and BA 40, or other cortical regions, including anterior cingulate, premotor and supplementary motor areas, and posterior parietal cortex (Smith and Jonides, 1998), ii) disrupted connectivity (i.e. white matter abnormalities) within the working memory network; iii) inefficient function of BA 46 in the face of structural integrity. In controls, larger left BA 46 volume was associated with *poorer* spatial working memory, but this association was insignificant with Bonferroni correction.

Summary: Overall, it appears that the archicortical PFC correlates most consistently with the tasks of executive function (Seidman et al., 1994; Szeszko et al., 2000), attention (Gur et al., 2000a), and verbal (Seidman et al., 1994; Maher et al., 1995; Gur et al., 2000a) and visual (Seidman et al., 1994) memory in schizophrenia, reflecting a normal pattern of structure/function relationships.

However, in the individual studies, the pattern of correlations between structural and functional measures appears to be different for patients and controls (Gur et al., 2002a), for men and women (Szeszko et al., 2000; Gur et al., 2002a), and might be attenuated in affected men (Gur et al., 2002a). There is also an indication of differential hemispheric involvement in the type of function, with left DLPFC being associated with abstraction/flexibility, categorization and non-verbal immediate memory, and right DLPFC being associated with sustained attention (Seidman et al., 1994). The paleocortex (OFC) appears to have a complex relationship with examined cognitive domains, perhaps due to an interaction between the nature of the task and the gender of the subjects (Seidman et al., 1994; Manschreck et al., 2000; Gur et al., 2000a).

Importantly, not all frontal functions seen to be impaired in patients were found to correlate with reduced total and regional PFC volumes in the reviewed studies (Gur et al., 2000a; Baare et al., 1999). Conversely, not all studies have found abnormal PFC volumes, while observing deficits in frontal function (Zuffante et al., 2001; Baare et al., 1999). Abnormalities in other brain regions might be contributing to the impaired performance on so called frontal measures in schizophrenia, as PFC function depends on the integrity of other cortical and sub-cortical structures that together constitute distributed functional networks, as has been noted in the introduction to this section.

2.5.4. Temporal Lobe

2.5.4.1. Introduction

Lateral structures of the temporal lobe include the superior temporal gyrus (STG), the middle temporal gyrus (MTG) and the inferior temporal gyrus (ITG). Medial temporal lobe structures include limbic structures such as the hippocampus/entorhinal cortex and amygdala, and paralimbic structures such as the parahippocampal gyrus (PHG).

Abnormalities in temporal lobe and deficits in memory observed in schizophrenia were linked together by Kraepelin (1919), who also considered temporal lobe to be a site of auditory hallucinations. Anatomical abnormality of left STG is indeed found in schizophrenia patients with auditory hallucinations (Barta et al., 1990), although not consistently (DeLisi et al., 1992). Overall, 67 % studies have found STG volume reduction in schizophrenia (Shenton et al., 2001), but this statistic goes up to 100% (10 studies) if only reductions in GMV are considered.

Reduction of the volume of hippocampal/amygdaloid complex is amongst the most replicable findings in schizophrenia research with 74 % replicability (Shenton et al., 2001) and is present in chronic as well as FE patients (Bogerts et al., 1990; Lawrie et al., 1999). None of the studies reviewed have looked at MTG or ITG, which are involved in auditory and visual processing respectively.

The studies that examined the whole temporal lobe (TL) are reviewed first, followed by those studies investigating the superior temporal gyrus (STG) and medial temporal lobe structures.

2.5.4.2. Whole Temporal Lobe

Thirteen studies measured the volume of the whole TL, ten with a control group or groups (DeLisi et al., 1991a; Di Michele et al., 1992; Hoff et al., 1992; Colombo et al., 1993; Flaum et al., 1994; Vita et al., 1995; Torres et al., 1997; Krabbendam et al., 2000; Gur et al., 2000b; Sanfilipo et al., 2002), and three without (Nestor et al., 1993; Seidman et al., 1994; Maher et al., 1995).

Only one study (Sanfilipo et al., 2002) found total TL volume reduction in patients relative to controls, which was limited to grey matter. Other studies did not observe TL reductions, perhaps due to the lack of segmentation into grey and white matter, or the insensitivity of the measurements in the earlier studies (DeLisi et al., 1991a; Di Michele et al., 1992; Hoff et al., 1992; Colombo et al., 1993; Vita et al., 1995; Sullivan et al., 1996), which used thick (5-6mm) slices.

Two studies observed positive associations between TL volume and cognitive functioning that were specific to schizophrenia (i.e. not seen in controls), including picture naming accuracy in chronic patients (Vita et al., 1995; also seen for the STG, see *section 2.4.2.*) and concentration/speed in FE patients (Hoff et al., 1992). Association with picture naming might be specific to the TL, as it has not been observed for the PFC (Vita et al., 1995).

One study (Flaum et al., 1994, see *Whole brain* section) reported a disrupted TL/cognition relationship in affected men, with greater bilateral TL volume associating with higher IQ in female patients and controls of both sexes, but not in male patients.

Other studies (DeLisi et al., 1991a; Di Michele et al., 1992, Seidman et al., 1994; Maher et al., 1995; Sullivan et al., 1996; Sanfilipo et al., 2002) reported no relationship between TL volume and specific deficits in schizophrenia, such as attention, abstraction/flexibility, verbal and nonverbal memory. In addition, Torres et al. (1997) did not find any difference in TL between patients who scored high or low on verbal and non-verbal memory tasks. There were no volume differences for high and low scoring controls either. Finally, Colombo and colleagues (1993) did not find TL size to be abnormal in patients with severe short-term memory and attention/concentration impairments. It is possible that deficits in abstraction/flexibility, memory and attention/concentration in schizophrenia are due to the PFC volume alterations, as reviewed earlier (Seidman et al., 1994; Szeszko et al., 2000; Gur et al., 2000a). Alternatively, more specific regions of TL might associate stronger with some of these cognitive processes, including learning and memory, and abstraction/flexibility, as reviewed further.

2.5.4.3. Superior Temporal Gyrus

Four studies have measured STG volume, three with a control group (Vita et al., 1995; Gur et al., 2000b; Sanfilipo et al., 2002), and one without (Nestor et al., 1993). Two studies (Gur et al., 2000b; Sanfilipo et al., 2002) have found reduction of STG grey matter in men, but not in women (Gur et al., 2000b). Vita et al. (1995) did not segment the STG into grey and white matter, which might explain their negative finding.

Greater left STG volume was associated with better verbal fluency and picture naming accuracy specifically in patients (Vita et al., 1995). In another study (Nestor et al., 1993), greater GMV of left and right posterior STG correlated with better abstraction/categorization, and greater GMV of left posterior STG with learning of verbal paired associations in male patients. The posterior STG, which includes Wernicke's area, is involved in language comprehension and semantic processing. Therefore, one interpretation of these findings, as suggested by the authors, is a dysfunction of the semantic system, which might underlie deficits in abstraction/categorization, picture naming, and semantic verbal fluency in schizophrenia. Sanfilipo et al. (2002), however, did not find either GMV or WMV of STG to associate with verbal fluency in the face of differential impairment of this function in their cohort of patients.

Other STG/cognition associations seem to be specific to controls. Greater STG volume was associated with greater processing speed (Sanfilipo et al., 2002), and

with spatial memory in healthy women and attention in healthy men (Gur et al., 2000b). It is possible that greater integrity/efficiency of semantic system associated with posterior STG volume would have a positive effect on cognition, particularly processing speed.

2.5.4.4. Medial Temporal Lobe

Parahippocampal gyrus (PHG) was measured in four studies, three with a control group (Krabbendam et al., 2000; Sanfilipo et al., 2002) or groups (DeLisi et al., 1991a), and one without (Nestor et al., 1993). None of the studies reported abnormal PHG volumes in patients. Hoff et al. (1992) measured the total volume of amygdala, hippocampus and PHG as a limbic complex and did not find it to be abnormal in FE patients.

Greater PHG volume was associated with higher verbal intelligence in both FE and chronic patients (DeLisi et al., 1991a) and in a separate sample of FE patients of mixed gender (Hoff et al., 1992). However, an inverse relationship between right PHG volume and verbal intelligence was found in male chronic patients (Sanfilipo et al., 2002). The later finding might reflect a disrupted relationship between structure and neurocognition in affected men, observed for other brain regions. Alternatively, larger right PHG volume might be indicative of the alteration of the normal, language related left-larger-than-right asymmetry of the posterior temporal lobe, manifesting as an inverse association between right PHG and verbal IQ in these male patients. Whatever the direction of this association, it seems to be specific to schizophrenia, as no relationship was found between PHG volume and verbal intelligence in normal controls in any of the studies. Other findings include an association of greater PHG volume with better performance on the color-word part of the Stroop test in chronic patients (Krabbendam et al., 2000); abstraction/categorization in male chronic patients (Nestor et al., 1993); associative learning in a mixed group of FE and chronic patients (DeLisi et al., 1991a); and memory for stories in FE patients (DeLisi et al., 1991a). None of these relationships were observed in healthy controls. Thus, it appears that, although not volumetrically abnormal, PHG has a number of associations with cognitive functions specific to schizophrenia.

The studies investigating the relationship between the hippocampus and amygdaloid/hippocampal complex and cognitive deficits outnumber the studies of any other specific brain region reviewed in this paper. One of the reasons for this interest is that the anatomic and functional affiliations of the limbic cortex in general, and the hippocampus in particular, can theoretically contribute to

clinical, psychophysiological and cognitive abnormalities observed in schizophrenia (Stevens, 1973; Torrey and Peterson, 1974; Weinberger and Lipska, 1995; Bilder and Szeszko, 1996). Moreover, animals with hippocampal lesions mirror the course and manifestation of schizophrenia with remarkable precision (reviews, Schmajuk, 1987; Lipska and Weinberger, 2002).

Ten studies measured hippocampus (DeLisi et al., 1991a; Colombo et al., 1993; Flaum et al., 1994; Nestor et al., 1993; Bilder et al., 1995; Torres et al., 1997; Gur et al., 2000b; Krabbendam et al., 2000; Szeszko et al., 2002; Sanfilipo et al., 2002). Out of six studies with a control group (DeLisi et al., 1991a; Colombo et al., 1993; Torres et al., 1997; Krabbendam et al., 2000; Gur et al., 2000b; Sanfilipo et al., 2002), only one has found reduction in the hippocampal GMV in affected men and women (Gur et al., 2000b). However, as hippocampal reduction might be limited to grey matter, other studies might have failed to find hippocampal abnormality due to the lack of segmentation. Also, the evidence for the hippocampal reduction is not as strong in FE patients as it is in chronic patients (DeLisi et al., 1991b).

Although not altered in most studies, hippocampal volume associated with different aspects of memory in patients, as well as in controls. In a study of monozygotic twins discordant for schizophrenia (Goldberg et al., 1994), greater left hippocampal intra-pair volume difference was associated with greater intra-pair difference in memory for stories. Gur and colleagues (2000b) have found greater bilateral hippocampus to be associated with better verbal and spatial memory in both men and women regardless of diagnosis. In contrast, Sanfilipo et al. (2002) have observed dissociation in the direction of correlations between patients and controls, such that left and right hippocampal volumes positively correlated with verbal memory in patients, whereas an inverse relationship between right hippocampal volume and verbal memory existed in controls. This finding is difficult to reconcile, especially considering that greater right hippocampal volume has also associated with better verbal fluency and Digit Symbol task performance in controls. These latter relationships were not present in the patient group, despite differential deficit of verbal fluency. Amongst negative findings in regards to memory function is the lack of any association between hippocampal volume and either verbal or visual memory in FE and chronic patients studied by DeLisi et al. (1991). Additionally, Torres and colleagues (1997) did not find hippocampal volume difference between patients differentiated by high and low ability of delayed memory, or between high and low performing controls.

Hippocampal volume has also been found to associate with the functions commonly attributed to the integrity of frontal lobes, supporting the notion that the deficits of higher order cognitive functions in schizophrenia might be due to the disruption of frontal-limbic circuitry (Lipska and Weinberger, 1995). Thus, two studies from the same laboratory (Bilder et al., 1995; Szeszko et al., 2002; the later study included a sub-sample of patients from the first study) reported positive correlations between anterior hippocampus and executive and motor functions in FE patients. In the earlier study (Bilder et al., 1995), correlations of hippocampal volume with executive, but not motor function, were significantly stronger than with full scale IQ. Also, there was no correlation of these cognitive domains with either posterior hippocampus or amygdala, suggesting the specificity of the observed association. There was no difference in the magnitude of this association between male and female patients. A later study (Szeszko et al., 2002) had a larger sample, and has observed significant differences in the strength of correlations between men and women with FE psychosis. In affected males, larger anterior hippocampus was associated with better executive and motor function, and significantly stronger than with memory or language. In affected females, no significant correlations were found, although there was a trend for an association between anterior hippocampus and memory.

Nestor et al. (1993) did not find any association between hippocampal volume and executive function in male chronic patients. This study measured abstraction and categorization aspects of executive function, whereas Bilder et al. (1995) and Szeszko et al. (2002) measured perseveration and inhibitory control. Thus, it is possible that only those measures of executive function that are indices of 'projectional control' are associated with hippocampal volume.

Finally, the amygdala was measured as a separate structure only by Gur and colleagues (2000b), who found reduced volume of the amygdala in men and increased volume in women with schizophrenia, but this was not associated with cognitive functioning either in patients or in controls.

Summary: The total TL volume is associated with picture naming (Vitta et al., 1995) and concentration/speed (Hoff et al., 1992). These associations might be specific to the TL and to schizophrenia. The GMV of the posterior STG might be associated with abstraction/categorization and verbal learning (Nestor et al., 1993), but the specificity of this association remains unclear. Hippocampal volume is associated with memory function in both patients and normal controls

of both genders (Gur et al., 2000b, but see DeLisi et al., 1991a). Finally, executive function requiring inhibitory control of behavior might be related to anterior hippocampal volume in schizophrenia (Bilder et al., 1995), particularly in affected men (Szeszko et al., 2002), whereas abstraction and categorization might be related to the volume of PHG (Nestor et al., 1993). PHG volume is also associated with a range of cognitive processes that might require access to a semantic system and this association might also be specific to schizophrenia (DeLisi et al., 1991a; Nestor et al., 1993; Krabbendam et al., 2002).

2.5.5. Posterior-occipital region

2.5.5.1. Introduction

The posterior part of the brain includes parietal and occipital lobes. The occipital lobe is dedicated to visual information processing, while the parietal lobe is a part of the heteromodal association cortex. Parietal association cortex is richly and reciprocally interconnected with PFC, temporal lobe and limbic cortex, forming cortico-cortical and cortico-subcortical functional networks with these regions (Mesulam, 1990, 1998). There are distinctly separate areas within the parietal lobe that are associated with different cognitive functions. In a very general sense, these include three main areas and functions. The postcentral gyrus contains primary somatosensory cortex, which is concerned with the initial stages of tactile and proprioceptive sensory processing. The inferior parietal lobule, usually of the left hemisphere, is involved in the language comprehension together with the posterior part of the temporal lobe. The remainder of the parietal cortex subserves complex aspects of spatial awareness and perception (Mesulam, 1998).

Shenton and colleagues (2001) identified 15 MRI studies that measured parietal lobe, 60% of which have found abnormal volume of this region. The abnormalities of subregions within the parietal lobe have also been reported, including reduced supramarginal gyrus (Goldstein et al., 1999), and inferior parietal lobule (Schaepfer et al., 1994). Only nine MRI morphological studies have measured occipital lobe, with 44 % of the studies reporting volume reduction in schizophrenia (Shenton et al., 2001).

2.5.5.2. Relationship of parieto-occipital region to cognition

Only one study (Sullivan et al., 1996, see also *FL* and *TL sections*) investigated functional correlates of the posterior brain regions. This study measured the volumes of parietal and parieto-occipital regions in 34 men with schizophrenia

and 47 healthy men. There were no significant differences either in GMV or WMV of these regions between the groups, and no significant correlations with four cognitive domains, which included executive function, verbal fluency, short-term memory, declarative memory and motor ability. Since the sub-regions of parietal lobe are functionally differentiated, global measurements of the posterior brain regions might have masked any specific associations with examined cognitive domains.

2.5.6. Basal Ganglia

2.5.6.1. Introduction

Basal ganglia (BG) is constituted by caudate nuclei (CN), nucleus accumbens (NA), putamen (Pu), globus pallidus (GP), substantia nigra (SNr) and subthalamic nucleus. CN and Pu are the sites of the input to BG from the multiple cortical regions, whereas GP and SNr are the sites of BG output. The interest in BG structures in relation to schizophrenia exists for the following reasons. First, the action of antipsychotic drugs primarily targets dopaminergic receptors that extensively innervate BG, particularly CN, NA and Pu. Second, there is a striking similarity between the symptoms observed in patients with nigral lesions and unmedicated first-episode schizophrenia patients, who frequently display 'soft' neurological signs, including: deficits in smooth pursuit eye movements and saccadic dysmetria; affective disturbances such as emotional blunting; altered perceptions such as hallucinations; and cognitive deficits (Middleton and Strick, 2000). Third, the role of BG in sensory, cognitive and motor functions in the context of fronto-striatal circuitry is important for understanding cognitive and clinical features of schizophrenia (Tekin and Cummings, 2002).

The kind of cognitive dysfunction that might be caused by abnormalities in BG structures might include executive function as well as learning and memory. Pantelis and colleagues (1997) have demonstrated that the nature of executive function in patients with schizophrenia resembles that of patients with frontal lobe lesions or basal ganglia dysfunction (Parkinson's patients), providing support for the notion that the nature of executive dysfunction in schizophrenia suggests the disturbance of fronto-striatal circuitry. Some memory and learning deficits in schizophrenia might also be due to fronto-striatal abnormalities (Beatty et al., 1993). This can be particularly the case with serial word-list learning, which was found to be impaired in patients with striatal dysfunction (e.g. Parkinson and Huntington disease) (Pillon et al., 1994). In fact, while normal subjects employ

the strategy of semantic clustering on word-learning tasks, both Parkinson and schizophrenia patients tend to depend on learning of serial word sequence (Shihabuddin et al., 1998). This serial learning strategy might depend more on striatal function than on hippocampal function (Poldrack and Packard, 2003).

Most studies (68%) report increases in the volumes of BG structures (Shenton et al., 2001). However, studies of FE patients have demonstrated volume decreases in CN and lenticular nuclei (LN = Pu + GP) (DeLisi et al., 1991a). Treatment with neuroleptics has been found to alter the volume of BG (Chakos et al., 1994). Shihabudin and colleagues (1998) have found smaller CN in never medicated patients and larger CN in previously medicated patients relative to normal controls. Moreover, while exposure to neuroleptics leads to the increased size of BG, treatment with atypical antipsychotic medication is shown to reverse this effect (Corson et al., 1999). Therefore, it is important to evaluate the effect of prior exposure to antipsychotic medication as well as medication type in the studies investigating BG abnormalities and their neuropsychological correlates.

2.5.6.2. Relationship of basal ganglia to cognition

Five studies have investigated cognitive correlates of BG. Three studies (DeLisi et al., 1991a; Flaum et al., 1994; Stratta et al., 1997) had a control group or groups while two did not (Maher et al., 1995; Manschreck et al., 2000).

In the most recent study, Stratta and colleagues (1997) investigated the hypothesis that executive dysfunction and disruption of goal-oriented behavior in schizophrenia is associated with striatal abnormalities. The total BG volume, the volume of the caudate nucleus (CN), and the joint volume of the putamen (Pu) and nucleus accumbens (NA) were measured in chronic patients and healthy controls (separate volumes of Pu and NA were only available for a sub-sample of patients). Patients were divided into poor and good performers based on their WCST categories completed score. No differences in age, duration of the illness or sex were found between poor and good performers. As hypothesized, poor performers had significantly smaller volumes of the BG structures, with the reduction of the total right striatum and left CN and Pu relative to normal controls, and left Pu and bilateral Pu-NA complex relative to good WCST performers. Good performers did not significantly differ from controls and, in fact, exhibited a trend for larger volumes of Pu and Pu-NA complex bilaterally. Striatal volumes in both good and poor performers were not related to the dosage of neuroleptic medication, which is known to alter the volume of BG structures

(Chakos et al., 1994). In patients, volumes of the left BG and Pu-NA complex positively correlated with the number of categories completed. In addition, unique errors on WCST inversely correlated with left Pu, NA, and Pu-NA complex. Perseverative errors did not significantly correlate with striatal volumes. As has been discussed in TL section, perseveration in schizophrenia might be related to the disruption of fronto-limbic circuitry (Bilder et al., 1995; Szeszko et al., 2000). It is unclear whether the found associations are specific to schizophrenia, as no correlations between WCST variables and striatal volumes were performed for the control group. Nevertheless, Stratta et al. (1997) provided support for the notion that the ability to organize goal-directed behavior is positively related to striatal volume in schizophrenia.

Flaum and colleagues (1994; see also *Whole brain*, *FL,* and *TL sections*) examined the volumes of CN and Pu in relation to the full scale IQ. The only association between the striatal volumes and IQ was the correlation of larger left Pu with higher full scale IQ in female patients, but not in male patients or normal controls. In fact, this correlation was the only one to significantly differentiate affected women from healthy controls.

DeLisi and colleagues (1991) measured the volumes of CN and the lenticular nuclei (Pu + globus pallidus) in FE and chronic patients, and neurological controls. Chronic patients had the largest CN volumes, while FE patients had the smallest, but neither group differed significantly from neurological controls. No significant correlations were found between the striatal volumes and cognitive measure, which included WCST and serial word learning, amongst others.

Two studies from the same laboratory (Maher et al., 1995; Manschreck et al., 2000; see also *Ventricular size*, *FL* and *TL volumes*) investigated the relationship between striatal size and the redundancy utilization ability, and observed an inverse correlation between striatal size and context-aided memory (Maher et al., 1995), but not motor-synchrony (Manschreck et al., 2000). It is possible that larger striatal volumes in Maher et al. study were associated with greater neuroleptic exposure, which, in turn, might be related to greater disease severity and hence poorer learning and memory, however no information was available on life-time neuroleptic exposure.

Finally, Jeste and colleagues (1998) investigated the relationship of structural and neuropsychological variables to the age of onset of schizophrenia (AOS). Although the structure/function examination was not the primary goal of the study, the

findings are interesting and relevant. Earlier AOS was associated with poorer abstraction/categorization, larger volumes of CN and LN, and smaller volumes of the thalamus. Despite the inter-domain correlations of neuropsychological and structural variables, there were no significant cross-domain correlations. When the authors performed a series of stepwise regressions with two-, three-, and four-variable models to predict the AOS in schizophrenia, they found that out of seven significant models, the model that accounted for the most variance (27.5%) included poorer learning, smaller thalamic and larger LN volumes as predictors. However, when the duration of illness, current age and current neuroleptic dosage were controlled for, the only model that remained significant included poorer abstraction/cognitive flexibility, smaller thalamus and larger CN.

Summary: There is some evidence for an association between striatal size and executive function in schizophrenia (Stratta et al., 1997; but see DeLisi et al. 1991; Jeste et al., 1998). However, there is no evidence for the positive association between striatal size and learning and memory from the studies reviewed, and in fact the inverse relationship might exist (Maher et al., 1995). Moreover, enlarged LN and poor learning might be associated with earlier disease onset (Jester et al., 1998). More studies are needed to investigate cognitive correlates of BG pathology, taking into account gender differences and exposure to neuroleptics. In particular, there is a lack of studies investigating the output site of BG, the globus pallidus. The function of globus pallidus interna might play an important role in the executive tasks associated with DLPFC function (Owen et al., 1996).

2.5.7. Thalamus

2.5.7.1. Introduction

The thalamus is a gateway to the cerebral cortex. It is a part of remarkably large number of pathways: all sensory pathways relay in the thalamus, and most of the anatomical circuits connecting neocortex with cerebellum, basal ganglia, reticular system and limbic structures path via thalamus. These various systems relay at the distinct locations of the thalamic nuclei. Due to this exceptional role as the relay station within the central nervous system, abnormality in the thalamus results in the information processing deficits. Some theories of schizophrenia aetiology concentrated on the dysfunction of thalamus and its role as a 'filter' for gating the sensory input as being at the core of symptomatology and cognitive deficits characteristic of schizophrenia (e.g. Jones, 1975, Frith and Done, 1989).

Several post-mortem studies have reported abnormalities in thalamic nuclei (reviewed by Heckers, 1997). MRI investigation of the thalamus in schizophrenia has been problematic in the past due to the difficulty in differentiating thalamic nuclei mass from the surrounding white matter. Nevertheless, there were at least 12 MRI studies of the thalamic volume in schizophrenia, 42% of which have found decreased volume and 58 % observed no differences between patients with schizophrenia and healthy subjects (Shenton et al., 2001). Reduced thalamic volume might be related to earlier onset of schizophrenia symptoms (Corey-Bloom et al., 1995; Jeste et al., 1998). In addition, smaller thalamic volumes were found to correlate with reduced volume of prefrontal white matter in schizophrenia patients (Portas et al., 1998).

2.5.7.2. Relationship of thalamus to cognition

Despite the theoretical and empirical implications of the thalamus as one of the sites of schizophrenia pathology, only one recent study (Saldago-Pineda et al., 2003) has examined the volume of the thalamus and found that reduction of left and right thalamic volumes did not correlate with the sustained attention deficit in patients (despite the association between the reduced thalamic grey matter concentration and sustained attention deficit; see **Experimental study 1: Introduction** for more detail). No correlation between thalamic volume and sustained attention performance in normal controls was observed either.

2.5.8. Cerebellum

2.5.8.1. Introduction

The cerebellum has been shown to be involved in higher cognitive functions, including learning and memory, planning, and language, amongst others (Leiner et al., 1991). The cerebellum receives input from the limbic lobe via hypothalamus and reticular nucleus, as well as neocortical areas via red nucleus and pontine nuclei. Cerebellar outputs project back to the limbic lobe via hypothalamus and reticular nucleus; and to motor cortex (areas 4 and 5), PFC (areas 8 and Broca's areas 44 and 45) as well as posterior lobe via thalamus (Leiner et al., 1991). On the basis of the connectivity between the posterior lobe, cerebellum and Broca's area, Leiner and colleagues (1989) proposed that the cerebellum might represent a link between the posterior (Wernicke's) and frontal (Broca's) language areas and contribute not only to the motor processes

necessary for the speech production, but also to the cognitive processes necessary for the choice of an appropriate word to express an idea. Support for this notion comes from the recent imaging studies that have shown striking activation in cerebellum during performance of mental tasks that require language processing (Peng et al., 2003; Xiang et al., 2003).

Schmahmann and Sherman (1997) have reported that lesions of cerebellum involving its posterior lobe and vermis were associated with impairments of working memory, planning, set shifting, verbal fluency, abstract reasoning, perseveration, visual-spatial disorganisation, visual memory deficits, logical sequencing as well as blunt or inappropriate affect. All these cognitive and affective disturbances are conspicuously characteristic of individuals with schizophrenia.

The evidence for the overall abnormality of the cerebellum is not very strong, with 31% reporting positive findings (Shenton et al., 2001). However, there is indication of abnormalities in the specific regions within the cerebellum such as reduced anterior vermis (Nopoulos et al., 1999; Levitt et al., 1999), posterior superior vermis (Okugawa et al., 2002) in male patients with chronic schizophrenia as well as decreased vermis-to-brain ratio in male patients compared to female patients (Rossi et al., 1993). The vermis is connected with the limbic cortex, including hippocampus and amygdala (Schmahmann, 1997), and thus might play a role in learning and memory.

Cerebellar abnormality might be limited to white matter. Two studies (Levitt et al., 1999; Seidman et al., 2000) have reported *increases* in cerebellar white, but not grey, matter volumes. As pointed out by Shenton and colleagues (2001), this increase in white matter might be the result of neuroleptic treatment, as there are findings of axonal sprouting in rats exposed to neuroleptic medication (Benes et al., 1983). Alternatively, this might represent a developmental abnormality. There is not enough evidence at present to discriminate between these alternatives. Finally, there is an evidence of progressive reduction in cerebellar hemispheric volume in schizophrenia patients (DeLisi et al., 1997b).

2.5.8.2. Relationship of cerebellum to cognition

Four studies (Flaum et al., 1995; Nopoulos et al., 1999; Levitt et al., 1999; Szeszko et al., 2003) have investigated cerebellar volume and its sub-regions and their relation to cognitive functioning in schizophrenia. All studies had a control

group, but two studies (Flaum et al., 1995; Szeszko et al., 2003) did not report on between-group morphological differences.

The total cerebellar volume was found to be unaltered in men with schizophrenia (Nopoulos et al., 1999; Levitt et al., 1999), but there was greater left-than-right cerebellar asymmetry of grey matter (Levitt et al., 1999). Cerebellar vermis, on the other hand, might be abnormal in affected men. Nopoulos and colleagues (1999) reported reduced volume of the anterior vermis, which was associated with lower full scale and verbal, but not performance, IQ. Levitt and colleagues (1999) reported increased vermal white matter, which was associated with poorer immediate memory for stories (Logical Memory). These associations between altered vermal volumes and cognition were specific to schizophrenia.

Other studies (Flaum et al., 1994; Szeszko et al., 2003) have observed a lack of cerebellum/cognition relationships in men with schizophrenia when such were found in normal controls. Flaum and colleagues (1994; see also *Whole brain*, *TL* and *BG sections*) found greater left and right cerebellar volume to be associated with higher IQ in normal men and women as well as in women with schizophrenia, but not in affected men, with this difference significantly differentiating affected men. Similarly, Szeszko and colleagues (2003) reported a positive correlation between total cerebellar volume and global neuropsychological functioning, visuo-spatial, and memory scales in healthy but not affected men, with the strength of the correlations being significantly different between the groups.

Summary: Men with schizophrenia might have cerebellar abnormalities that are limited to the anterior vermis (Nopoulos et al., 1999) and an increase of white matter (Levitt et al., 1999), which are associated with lower general and verbal ability and the dysfunction of narrative memory respectively. Total cerebellar volume does not seem to be altered and does not associate with cognitive ability in affected men. In healthy people (Flaum et al., 1994; Szeszko et al., 2003) and women with schizophrenia (Flaum et al., 1994), on the other hand, total cerebellar volume bares positive association with cognitive ability.

2.5.9. Midbrain

2.5.9.1. Introduction

The midbrain is of a particular interest in schizophrenia as it contains the source nuclei of three dopaminergic pathways in the human brain: the nigrostriatal pathway, originating in SNr; the mesolimbic pathway and the mesocortical pathway, both originating in the ventral tegmentum. Due to the association with dopaminergic pathways and the mediatory position of the midbrain between the cerebrum and the cerebellum, midbrain abnormality would be expected to have an implication for a range of cognitive functions as well as affective processing related to the dopamine transmission.

Despite this significance of the midbrain in schizophrenia, there has been only one morphometric study (see below) investigating this brain region. One histological study (Bogerts et al., 1983) has found a significant decrease in the volume of the nigrostriatal system due to the reduced volume of glial nuclei, as well as a decrease in the number of nerve cells in the mesolimbic system in never-medicated schizophrenia patients. In addition, Minabe and colleagues (1990) described a case of a 40-year-old woman who had developed a syndrome consistent with schizophrenia diagnosis following midbrain tegmental lesion.

2.5.9.2. Relationship of midbrain to cognition

Nopoulos and colleagues (2001) investigated midbrain volume and its relationship with IQ. The midbrain, as well as pons and medulla as control regions, were measured in 50 men with schizophrenia and 50 healthy men. Midbrain volume, but not pons or medulla, was significantly smaller in affected men, but the volume reduction was not associated with lower IQ.

2.5.10. Corpus Callosum

2.5.10.1. Introduction

The corpus callosum (CC) is a bundle of white matter tracts that connects two hemispheres. It allows the integration of cerebral hemispheric activity for higher cognitive function (review, Hoptman and Davidson, 1994). Defective interhemispheric communication mediated by CC was proposed to underlie information processing deficits characteristic of schizophrenia (Coger and Serafetinides, 1990).

An initial finding of a thicker CC in post-mortem study of schizophrenia patients (Rosenthal and Bigelow, 1972) led to the surge of interest in this structure with the advent of *in vivo* imaging techniques. Following the initial replication of the findings with MRI (Nasrallah et al., 1986), subsequent studies produced conflicting results, reporting no abnormality or a reduction of the CC area (meta-analysis, Woodruff et al., 1995). Overall, 63% (17 out of 27) of the studies reported abnormal corpus callosum in schizophrenia, with the variability in measuring methods being the strongest possible contributor to the inconsistency of the findings (Shenton et al., 2001).

2.5.10.2. Relationship of corpus callosum to cognition

Four studies investigated the relationship between CC and cognitive functioning in schizophrenia (Raine et al, 1990; Hoff et al., 1994; Woodruff et al., 1997a; Rossell et al., 2001), all with the control group or groups.

Raine and colleagues (1990) investigated structural and function characteristics of the CC in schizophrenia patients, psychiatric controls and normal controls. They have measured the total area and length of the CC as well as thickness of its anterior, middle and posterior segments. Dimorphic gender presentation of the anterior and posterior callosal thickness was evident in schizophrenia patients, such that normal male controls had thicker callosi than female normal controls, whereas this gender difference was reversed in the patient groups. There was, however, no difference between two groups in the inter-hemispheric function thought to be mediated by the CC.

Hoff and colleagues (1994) used a comprehensive neuropsychological battery to investigate the relationship between the CC size and domains of higher cognitive function in first episode schizophreniaform patients and normal controls. They observed smaller total CC area in female patients relative to female controls and male patients. Total CC size positively correlated with executive functioning, verbal memory, speed of information processing, sensory/perceptual function, right hemisphere function, and the global function in normal controls with similar correlation strength observed for men and women. However, these CC/function relationships were disrupted in FE patients, with negative non-significant correlations.

Woodruff et al. (1997a) studied the relationship between total CC area and four CC segments and inter-hemispheric function as measured by the modified version of the Stroop task (Philips et al., 1996). They did not observe any significant

differences in total CC or its sub-areas between chronic schizophrenia patients and normal controls. Patients, however, showed less interference on the task. Both bilateral facilitation and bilateral interference performance indices correlated with the posterior CC segment at a trend level in schizophrenia patients, such that better performance was associated with larger posterior CC area. However, these relationships were much weaker in controls.

Finally, Rossell et al. (2001) investigated the relationship of total CC area and length, as well as the areas of four CC segments, to the performance on dichotic listening and finger tapping tasks in chronic schizophrenia patients with and without the history of auditory verbal hallucinations and normal controls. There was no difference between the groups on any of the CC measurements. Both patient sub-groups performed significantly worse than normal controls on finger tapping task. There was no relationship between CC measurements and neuropsychological performance in either patient or controls.

Summary: The findings pertaining to the relationship between structure and function of the CC are inconsistent in both schizophrenia patients and healthy individuals. Three studies investigated the relationship between CC and inter-hemispheric transfer, with two observing no relationship either in patients or controls (Raine et al., 1990; Rossell et al., 2000), and one study noting a trend association specific to patients (Woodruff et al., 1997a). The study using standard neuropsychological tests of presumably lateralised higher cognitive functions (Hoff et al., 1994) observed a reverse pattern, such that larger CC had a positive effect on cognition in healthy individuals, but not in patients with schizophrenia, for whom larger CC size was associated with worse performance.

2.5.11. Brain asymmetry and cognitive function

2.5.11.1. Introduction

In addition to the evidence of the altered whole brain volume and specific brain regions and the relationship of these alterations to cognitive deficits in schizophrenia, there is also an issue of altered brain asymmetry in schizophrenia and its bearing on cognitive processes.

Although not a uniquely human characteristic (Rosen, 1996), brain asymmetries tend to associate with lateralisation of specific functions across species (Harris et al., 1996). One cognitive function that is specifically human is language.

Language in humans has been linked to the left hemisphere since the time of Broca (1861), who reported that left hemispheric lesion leads to speech disturbances. Overall, there is right-left (right larger than left) hemispheric asymmetry in normal human brain. However, for the area that has been linked to language function, Planum Temporale (PT), which lies at the posterior border of STG, the reverse asymmetry is observed. Thus, there is left – right (left larger than right) asymmetry in 65 % of the normal human brains, while 35 % have equal or larger right than left PT (Geschwind and Levitsky, 1968). Other normal brain asymmetries in humans include right-left asymmetry of the frontal lobe and left-right asymmetry of the occipital lobe (Galaburda et al., 1978).

Brain asymmetry is modulated by gender (McGlone, 1997) and handedness (Annet and Alexander, 1996). It has been hypothesised that formation of normal human brain asymmetries has genetic underpinnings (Geschwind, 1978) and that schizophrenia might be a result of an abnormal formation of language related cerebral asymmetries (Crow, 1989, 1990, 1993, 1995). At least some patients with schizophrenia show the reverse asymmetry of language related areas, with five out of 10 studies reporting larger right than left PT (Shenton et al., 2001). Abnormalities in PT asymmetry are found to associate with clinical features, such as suspiciousness/persecution subscales of the Positive and Negative Symptom Scale (Kay et al., 1987) and formal thought disorder (Rossi et al., 1994; Petty et al., 1995). The evidence for disrupted asymmetries of frontal and occipital lobes in schizophrenia is more modest. As reviewed by DeLisi and colleagues (1997), one study out of five, which compared the width asymmetries of frontal and occipital lobes of patients with schizophrenia with that of controls, has observed the reversed frontal asymmetry (Lee et al., 1985), whereas another study (Luchins et al., 1979) reported reversed occipital asymmetry in schizophrenia. The authors of the later study have subsequently failed to replicate this finding (Luchins and Meltzer, 1983). However, in both studies by Luchins and colleagues, altered occipital asymmetry was associated with greater psychopathology on measures of quality of interview, incomprehensibility, and auditory hallucinations.

2.5.11.2. Relationship of brain asymmetry to cognitive function

Two studies (Hoff et al., 1992; DeLisi et al., 1997a) have directly investigated the effect of disrupted brain asymmetries on cognition in schizophrenia.

Hoff and colleagues (1992, also see *Ventricular size* and *TL sections*) measured the length of the lateral sulcus (LS), which corresponds to the length of the

planum temporale (PT) (posterior area associated with language) in a mixed gender sample of FE patients and normal controls. A lack of normal left/right LS asymmetry was found in female, but not male, patients. Surprisingly, a sub-group of patients with the lack of normal asymmetry demonstrated *better* global, executive, verbal and spatial memory functions than the sub-group with normal asymmetry. Language functioning, however, was not related to the degree of LS asymmetry in patients. For the control group, there were no differences in cognitive performance between the abnormal and normal asymmetry sub-groups.

DeLisi and colleagues (1997) assessed neuropsychological correlates of the frontal, temporal, and occipital asymmetries, as well as the segments of sylvian fissure (anterior, horizontal, and vertical) in FE patients and normal controls. Both male and female patients had reduced left/right asymmetry of the temporal and occipital lobes. Surprisingly, the degree of left/right occipital asymmetry was inversely correlated with the complexity of expressive language. A trend for a reduction of left hemisphere length as well as reduced left/right asymmetry of the horizontal segment of SF (overlying PT) was also observed. However, the degree (reversed, reduced, or normal) of laterality of this region, hypothesized to be crucial for language, did not associate with language disturbances, but related to vigilance (sustained attention). Vigilance was also positively correlated with the degree of left/right asymmetry of the anterior sylvian fissure. Normal subjects exhibited a different and an extensive pattern of correlations between the degree of brain asymmetries and cognition. Left/right asymmetry of the horizontal sylvian fissure segment correlated positively with receptive language performance in a noise distraction condition, but inversely in a quiet condition. In addition, greater asymmetry of this region associated with better nonverbal memory. Greater posterior frontal and anterior sylvian fissure asymmetries associated with better phonological verbal fluency. Greater right/left anterior frontal asymmetry associated with better verbal memory and non-verbal ability. Finally, greater left/right temporal asymmetry associated with better verbal memory. None of these relationships survived a correction for multiple comparisons either in patients or in controls.

Summary: The current evidence points towards reduced asymmetry of the language related areas in FE patients, but does not support its hypothesized association with language disturbances. In healthy individuals, normative asymmetry of language related areas appears to associate with a range of cognitive domains, including language.

2.6. Summary of the main findings and patterns

There has been some consistency in structure/function relationships in both schizophrenia patients and healthy individuals. In general, total brain volume tends to have a non-specific relationship with cognition, with bigger brains associating with better performance. Similarly, measures of general cognitive ability, such as IQ, tend to correlate with a number of brain regional volumes, including left and right cerebral hemispheres, hippocampus, and cerebellum in normal controls and female patients, but these relationships might be disrupted in men with schizophrenia (Flaum et al., 1994). Since the frontal lobe has a unique involvement in higher cognitive processing and behavioral control, the volume of dorsal PFC, particularly its grey matter, is positively correlated with a range of cognitive processes in both patients and controls, including abstraction, attention, verbal memory, and psychomotor speed (Gur et al., 2000a; Sanfilipo et al., 2002).

A number of associations appear to be specific to schizophrenia. Greater cognitive flexibility in patients associated with greater GMV and particularly WMV of the PFC (Nestor et al., 2002; Sanfilipo et al., 2002), as well as smaller 3rd ventricle VBR (Bornstein et al., 1992). These associations indirectly implicate the role of fronto-thalamic circuitry in cognitive flexibility in schizophrenia. Other specific associations suggest that the dysfunction of language, as well as higher cognitive processes that require verbal endowment and abstraction/categorization of verbal information, might be associated with the volumes of STG and PHG (DeLisi et al., 1991a; Hoff et al., 1992; Nestor et al., 1993; but see Sanfilipo et al., 2002).

Reviewed findings suggest that executive dysfunction in schizophrenia might be associated with the volumes of several distributed structures apart from the PFC. Executive tasks normally engage a number of distinct processes and abilities: i) identification and categorization of information relevant to the task, ii) development of a strategy or acquisition of a rule necessary for the task performance; and iii) inhibition of pre-potent yet redundant responses. The data from the reviewed studies suggest that the first ability might be related to the volumes of PHG and STG and the function of semantic system associated with these regions (Nestor et al., 1993). Second ability might be related to the integrity of the striatum (Stratta et al., 1997). In fact, recent modeling work suggests that hierarchical updating and the sequencing of actions may involve

interactions between the PFC and the basal ganglia (Houk and Wise, 1995). Finally, the third ability might be dependent on the integrity of the anterior hippocampus (Szeszko et al., 2002) and the AC (Szeszko et al., 2000). Abnormality in this fronto-hippocampal circuitry might result in a failure of error detection/inhibition in schizophrenia, leading to perseveration. Possible thalamic abnormality and deficits in 'set shifting' associated with fronto-thalamic interaction might also disrupt the third ability (Bornstein et al., 1992). All these neuronal circuits have been implicated in the models of schizophrenia pathophysiology (see *section 1.3*.). It must be acknowledged, however, that these functional distinctions mapped onto different neuronal circuits are only heuristics.

Discrepancies between patients and controls in the pattern of structure/function correlations were present in most studies. These differences might represent statistical artifacts, altered structure/function relationship in schizophrenia, or an interaction of both. For example, relative task difficulty and relative structural volume variability would produce different ranges of scores and volumes in two groups for the same set of structural/functional variables, resulting in correlations of a different strength. In order to account for this possibility and to aid the interpretation of the findings, future studies should report on structural and functional differences between the groups and examine relative variability of performance and volumetry before proceeding towards the examination of structure/function relationship. In other cases, however, differences in structure/function relationship between patient and controls might reflect a genuine finding. However, only few studies have tested whether such between-group correlation differences were significant, with other studies leaving the implications of their findings unclear. Future studies should not only investigate the relationship between structural alterations and cognitive deficits but also ascertain whether there is an altered structure/function relationship in schizophrenia.

CHAPTER 3. SCHIZOPHRENIA: TREATMENT AND THE PREDICTION OF TREATMENT RESPONSE

In this chapter, the pharmacological treatments of schizophrenia will be introduced, namely typical and atypical antipsychotics. The distinction between two groups of antipsychotics in terms of their pharmacology as well as their clinical, side-effects, and cognitive profiles will be made. These will be followed by the presentation of differences within the atypical antipsychotic group in terms of their pharmacological properties, and the putative mechanisms underlying superiority of atypical action on symptoms and cognition in schizophrenia. Further, the empirical evidence for the clinical and cognitive superiority of the atypical antipsychotics under investigation will be presented. The chapter is concluded with the issue of predicting antipsychotic drug response.

3.1. Pharmacological Treatments of Schizophrenia: Typical and Atypical Antipsychotics

Conventional, or typical, antipsychotics were discovered in the 1950s and immediately became a first line of treatment for schizophrenia. Their ability to reduce positive symptoms gave them the name 'antipsychotic'. Recently, a new generation of drugs was developed which rapidly became preferred treatment in first-episode psychosis as well as in treatment-resistant schizophrenia.

Newer antipsychotic drugs were developed in response to problems with typical antipsychotics (see next *section 3.1.1.*). These drugs were referred to as 'atypical' as they did not produce catalepsy in rodents as all conventional, typical, antipsychotics do, while still having antipsychotic effects (Pilowsky, 2001). The ability to induce catalepsy was used as a screening tool for antipsychotic drugs and was believed to be necessary for a drug to have an antipsychotic effect. Thus, initially, atypical antipsychotics were defined as those antipsychotic agents

which produce fewer extrapyramidal symptoms (EPS) at clinically effective antipsychotic doses than the typical antipsychotics (Meltzer et al., 1999).

However, this definition of an atypical antipsychotic drug is still controversial (Gerlach & Casey, 1996). Various authorities have suggested that the term is to be changed to 'novel antipsychotics', while others suggested for the definition to be broadened to include features beyond lower EPS, such as multireceptor affinity, efficacy in treatment-resistant schizophrenia, and ability to improve negative as well as cognitive symptoms (see Kinon and Lieberman, 1996 for a critical discussion).

Clozapine is the first prototype of an atypical antipsychotic drug and has been shown to have all of the above-mentioned characteristics (e.g., Arnt and Skarsfeldt 1998; Remington and Kapur, 1999). It became a drug of choice for treatment resistant schizophrenia. However, it has serious side effects such as agranulocytosis, which limits its applicability in the treatment of psychosis. Therefore, there was a need for developing other atypical antipsychotic agents with similar efficacy, but without serious life-threatening side effects. *Olanzapine*, *Risperidone* and *Quetiapine* are atypical antipsychotics that have been developed to address these demands. The following discussion of atypical antipsychotics is going to be restricted to these three brands, since they are the most commonly used in current clinical practice.

3.1.1. Typical Antipsychotics

Discovery of neuroleptics revolutionised the treatment of schizophrenia and brought an emphasis on the positive symptoms, which the typical antipsychotics so dramatically reduce. Treatment with typical antipsychotics led to the closing of hospitals for most chronic psychiatric patients and offered much hope for the patients to be reintegrated into the society. However, by the 1960s it became obvious that reduction in positive symptoms did not lead to recovery from schizophrenia. Although typical antipsychotics were effective in treating positive symptoms, they lack the ability to improve cognitive impairment (e.g. Medalia et al., 1988) and thus produce poor functional outcome (Meltzer & McGurk, 1999).

Moreover, typical antipsychotics have further problems such as lack of efficacy in one third of the patients (Friedman et al., 1999), lack of improvement and even worsening of negative symptoms (Sharma, 1999), and troublesome adverse

effects, especially EPS and tardive dyskinesia. The most common treatment of EPS is co-administration of drugs with strong anticholinergic properties. These agents cause further problems for patients with schizophrenia by impairing their already compromised cognitive functions (e.g., Strauss et al., 1990; Kumari et al., 2003b; Ettinger et al., 2003), and thus reducing the prospects for positive functional outcome (Green, 1996).

Conventional antipsychotics are non-selective dopamine antagonists with mainly D2 receptor affinity. The ability of conventional antipsychotics to block D2 receptors in the mesolimbic pathway such as nucleus accumbens and olfactory tubercle appears to be the basis for their effect on positive symptoms (Meltzer & Stahl, 1976). Blockade of D2 receptors in the striatum appears to be the basis for the EPS (Meltzer & Stahl, 1976).

3.1.2. Atypical Antipsychotics

The class of drugs refered to as atypical antipsychotics includes drugs with heterogeneous pharmacological makeup. However, as a class, atypical antipsychotics differ from typical ones on one crucial property: their limbic-specific dopamine D2 receptor binding and high ratio of serotonin 5-HT 2 receptor binding to D2 binding (Arnt and Skarsfeld, 1998).

Despite the controversies in defining the atypical drug, there is a general agreement that three features differentiate the atypical antipsychotics from the conventional ones, and that these features may arise from the dopamine - serotonin antagonism which most of the atypical antipsychotics share (Meltzer & McGurk, 1999). The first of these differentiating features, as mentioned above, is that the atypical antipsychotics show little or no propensity to cause EPS or tardive dyskinesia, which are the most troublesome side effects of the conventional antipsychotics.

The mechanism by which atypical antipsychotics spare the motor function is related to the reciprocal relationship between serotonin and dopamine in nigrostriatal pathway that projects from substantia nigra to the striatum and regulates movement. The nature of this relationship is such that serotonin inhibits dopamine release (Meltzer, 1991). Thus, serotonin antagonism of atypical antipsychotics in nigrostriatal pathway disinhibits dopamine neurones. The dopamine released through disinhibition competes with the atypical drug for

the D2-receptors and thus does not lead to their total inhibition, as it is the case with the conventional antipsychotics. Thus, serotonin blockade reverses D2 blockade in the striatum, which is the cause of little or no extrapyramidal effects and tardive dyskinesia with atypical medication (Kapur & Remington, 1996).

The lower affinity of atypical antipsychotics to striatal D2 dopamine receptors is another possible reason for the low EPS incidence with these newer drugs as compared with conventional antipsychotics (Pilowsky, 2001). The lower occupancy of striatal D2 receptors allows for dopamine to compete with the atypical drug at the D2 receptor sites, while occupancy of D2 receptors with conventional antipsychotics can be as high as 80 % (Stahl, 1998) resulting in complete inhibition of the D2 receptor neurons and thus to the EPS.

Second differentiating feature of atypical antipsychotics is that some of them do not raise prolactin levels, which every conventional antipsychotic does (Kapur & Remington, 1996). This property of atypical antipsychotics might be due to reciprocal relationship of serotonin and dopamine in tuberoinfundibular pathway that projects from hypothalamus to the pituitary (Stahl, 1998). Dopamine inhibits prolactin secretion in the pituitary (Kapur & Remington, 1996). D2 antagonism of conventional drugs leads to the blockade of the D2 receptors, which results in increased prolactin levels. In contrast to dopamine, serotonin stimulates prolactin secretion, when it occupies 5HT-2 receptors and excerpts an indirect action on dopamine, by preventing dopamine release. 5HT-2 antagonism of atypical antipsychotics leads to the blockade of 5HT-2 receptors and thus reverses the effects of blocking D2 - receptors, leading to the release of dopamine and allowing for the dopamine inhibition of prolactin secretion to take place (Bouloux & Grossman, 1987). This makes serotonin-dopamine antagonists better tolerated than conventional antipsychotics, which may have an indirect effect on cognitive improvement (Meltzer & McGurk, 1999).

Finally, most atypical antipsychotics reduce negative symptoms of schizophrenia and have positive effects on cognitive deficits to a greater extent than the conventional antipsychotics (e.g. Hagger et al., 1993; Hoff et al., 1996; Green et al., 1997; Rossi et al., 1997). Also, there is some evidence for atypical antipsychotics to be superior to conventional antipsychotics in improving automatic information processing deficits as assessed by pre-pulse inhibition (PPI) of the startle response in schizophrenia (Kumari et al., 1999, 2000, 2002b; Leumann et al 2002).

The mechanism by which atypical antipsychotics have ameliorating effect on negative symptoms and cognitive impairments may be related (Arnt et al., 1999). The revised dopaminergic hypothesis of schizophrenia proposes the coexistence of a hyperdopaminergic state in the mesolimbic pathway, underlying positive symptoms, along with hypodopaminergia in the mesocortical tract (Davis et al., 1991; O'Donnell and Grace, 1998; Weinberger, 1987). Primary deficiency of dopamine in the mesocortical pathway, which projects from midbrain ventral tegmental area to limbic cortex, is a hypothetical cause of negative symptoms and some of the cognitive symptoms. Secondary deficiency of dopamine in the mesocortical pathway as a result of serotonin excess is another hypothetical cause of negative and cognitive symptoms in schizophrenia (Goldberg & Weinberger, 1996). Serotonin-dopamine antagonists, but not conventional antipsychotics, can increase dopamine release and decrease levels of serotonin selectively in the mesocortical pathway by blocking 5-HT2 receptors (Fischman et al., 1996). This theoretically explains the improved efficacy of atypical antipsychotics over conventional antipsychotics in the treatment of negative and most of the cognitive symptoms of schizophrenia (Friedman et al., 1999).

3.1.3. Pharmacological profile of atypical antipsychotics

Atypical antipsychotics have the most complex mixture of pharmacological properties in psychopharmacology (Stahl, 1998). These agents act on multiple DA receptors (D1-4), serotonin receptors (5-HT -1A, 2A, 1D, 3, 6, 7) and serotonin reuptake inhibition, noradrenergic system (alpha 1 and alpha 2 blockade), cholinergic system (muscarinic blockade and norepinephrine reuptake inhibition), and histamine (H1) receptors.

TABLE 3.1. Pharmacological profile of olanzapine, risperidone and quetiapine

Olanzapine:	**Risperidone:**	**Quetiapine:**
D1-4	D2	D2
5-HT2a	5-HT2a	5-HT2a
5-HT2c		
5-HT3		
5-HT6		5-HT6
	5-HT7	5-HT7
M1		
H1	H1 (?)*	H1
α 1	α1 and α 2	α1 and α 2

* See text

Table 3.1 presents the pharmacological profile of the atypical drugs most commonly used in clinical practice. As can be seen from the table, *olanzapine* has the most diverse repertoire of neuroreceptor affinity. It antagonises dopamine receptors D1-4, four subtypes of serotonin receptors, 5-HT -2a, -2c, -3 and -6, muscarinic receptor M1, histamine receptor H1 and has affinity to α1-adrenergic receptor. *Risperidone* differs from *olanzapine* in that it has affinity to only D2 dopamine receptor, two serotonin receptor subtypes, 5-HT 2a and -7, and α1 and α 2- adrenergic receptors. Different studies and reviews are inconsistent in regard to *risperidone's* affinity to H1 histamine receptors. It does appear, though, that its action on these receptors is not as potent as that of *olanzapine* and *quetiapine*. *Risperidone* does not have affinity to muscarinic receptors. *Quetiapine* is very similar to *risperidone* in its pharmacological profile. The only additional property is antagonism of serotonin 5-HT6 receptor subtype.

Recent PET studies of D2 and 5-HT2a blockade by *olanzapine*, *risperidone* (Kapur et al., 1999) and *quetiapine* (Kapur et al., 2000) have revealed that *quetiapine* has the lowest affinity to these receptors and shortest half-life then the other two atypical antipsychotics. *Risperdone* and *olanzapine* were found to have similar affinities to D2 and 5-HT2 receptors, with *risperidone* having a slightly higher occupancy of D2 receptor then *olanzapine* at clinically relevant doses. These pharmacological differences may account for differential clinical and side-effect profiles of these atypical antipsychotics (Remington and Kapur, 2000) and will be discussed in the following sections.

3.1.4. Atypical antipsychotics: Effects and putative mechanisms of action on symptoms and cognition

As discussed above, one mechanism for their superior effect on cognitive deficits is serotonin-dopamine antagonism that all atypical antipsychotics share. Serotonin-dopamine action in mesocortical pathway can have direct ameliorating effect on cognitive deficits by mediating dopamine and serotonin transmission in prefrontal cortex (Meltzer and McGurk, 1999). Also, serotonin-dopamine action of atypical antipsychotics can play an indirect role in cognitive enhancing effects as compared with conventional antipsychotics through greater reduction in primary and secondary negative symptoms, adverse side effects, such as EPS and hyperprolactinemia, and increased tolerability (Keefe et al., 1999).

Other receptor-binding properties may be involved in efficacy of atypical antipsychotics on cognitive impairments in schizophrenia. The combination of simultaneous actions may be required to explain the mechanism of enhanced efficacy of atypical drugs on cognitive functions as compared to conventional antipsychotics. Thus, some of the beneficial effects of serotonin antagonism of the atypical drugs may be mediated through the effect of serotonin neurones on cholinergic neurones (e.g., Decker and McGaugh, 1991). 5-HT antagonists have been shown to alter the detrimental effects of muscarinic cholinergic antagonists on learning and memory (Keefe et al., 1999). Anticholinergic properties of conventional antipsychotics have been shown to worsen learning and memory in patients with schizophrenia in many studies (review, Heaton and Crowley, 1981). *Olanzapine* has anticholinergic properties, but does not seem to affect learning and memory (Keefe et al., 1999). This may be due to its high affinity to both cholinergic and serotonergic neuroreceptors, as serotonin antagonism may cancel out the detrimental memory effects of cholinergic antagonism (Keefe et al., 1999).

3.1.5. Atypical antipsychotics: Preliminary evidence of clinical and cognitive superiority

3.1.5.1. Clinical efficacy

Overall, there is consistent evidence that *olanzapine*, *risperidone* and *quetiapine* are at least as effective and, in the case of non-responders, superior to conventional medication in the treatment of positive symptoms in schizophrenia (Mortimer, 2001). Also, these drugs have been found to be more effective than conventional medication for the treatment of both primary and secondary negative symptoms at clinically effective doses, although the evidence is stronger for *olanzapine* than either *risperidone* or *quetiapine* (review, Remington and Kapur, 2000).

Olanzapine, *risperidone* and *quetiapine* have a record of better tolerability in terms of side-effects such as EPS, tardive dyskinesia and hyperprolactinemia, although there are higher incidence of these side effects with *risperidone* than with *olanzapine* or *quetiapine* (Remington and Kapur, 2000). However, as discussed by Kapur et al. (1999), these differences might have emerged due to the clinical doses of *risperidone* used that produce higher D2 receptor occupancy

then the doses used for *olanzapine* or *quetiapine*, and thus higher levels of EPS and hyperprolactinemia were found for *risperidone* in the previous studies. It is also possible that the higher incidence of EPS and hyperprolactinemia with *risperidone* is due to lower 5-HT2/D2 ratio as compared to *olanzapine* or *quetiapine*, as the D2 receptor affinity has been reported to be higher for *risperidone* then for *olanzapine* or *quetiapine* (Kapur et al., 2000), while 5-HT2 receptor affinity of *risperidone* and *olanzapine* has been reported to be similar (Kapur et al., 1999).

3.1.5.2. Cognitive efficacy

The atypical antipsychotics have been shown to produce greater improvement in cognitive deficits when compared with conventional drugs (review, Meltzer & McGurk, 1999, Keefe *et al*., 1999, Sharma, 1999). When compared as a group with conventional antipsychotics in meta-analysis of data from 15 studies (Keefe et al., 1999), atypical antipsychotics were found to be superior in their cognitive enhancing effects in at least one cognitive domain in two of three double-blind studies and in seven of the 12 open-label investigations.

In the review of cognitive effects of atypical antipsychotics by Meltzer and McGurk (1999), *risperidone* has been found to improve performance on measures of attention, executive function, working memory, verbal learning and memory, motor function and perceptual/motor processing, but not verbal fluency or motor learning. *Olanzapine* has been found to have significant effect on some measures of reaction time, executive function, verbal learning and memory, and verbal fluency. The magnitude of this effect for *olanzapine* was greater than that previously found for *clozapine* or *risperidone* (Meltzer and McGurk, 1999).

In a recent 6-months study of cognitive effects of *risperidone* and *olanzapine* in the group of 38 partially responsive outpatients with schizophrenia, atypical antipsychotics were associated with significant differential improvement over time in attention, verbal memory and executive function as compared to conventional antipsychotics. No improvement has been found on measures of verbal fluency, spatial memory and visuo-motor abilities (Cuesta et al., 2001). *Risperidone* and *olanzapine* had differential effect on measures of cognitive function, with *risperidone* being superior on measures of executive function (Wisconsin Card Sorting Task) and *olanzapine* having greater effect on selective attention (Stroop test).

In a recent independent, randomised, double-blind study (Purdon et al., 2001), *quetiapine* has been found to improve verbal fluency and immediate recall. In another larger, randomised, double-blind trial of 41 stable outpatients, *quetiapine* was found to be superior than haloperidol on tests of executive function and verbal memory (Velligan et al., 1999).

3.2. Prediction of Treatment Response

Patients with schizophrenia vary considerably in their response to antipsychotic medication. Only one third will be responsive to the treatment with conventional antipsychotics, with higher percentage of responders to novel atypical drugs. Since it became evident that schizophrenia is characterised by global as well as regional structural volume alterations, the question has arisen as to how the degree of structural alterations is related to drug response. Crow (1985) initially hypothesised when defining Type I and Type II schizophrenias that patients with Type II illness will have enlarged ventricles and will be characterised by the poor response to antipsychotic drug treatment. Subsequent studies relating ventricular size to treatment response yielded inconsistent results: whereas some studies confirmed larger ventricular size to result in poorer drug response (Nasrallah et al., 1980; Weinberger et al., 1980; Luchins et al., 1983, 1984; Williams et al., 1985; Pandurangi et al., 1989), others have not observed such an association (Nasrallah et al., 1983; Naber et al., 1985; Losonczy et al., 1986) and even reported reverse findings (i.e. larger ventricles predicting better response) (Boronow et al., 1985; Smith et al., 1985).

There is a paucity of studies investigating the relationship between global or local tissue volumes and the neuroleptic drug response, with only one MRI study up to date examining the possibility of such a relationship. Zipursky and colleagues (1998) studied structural correlates of drug response in first episode patients and reported that the severity of cortical grey matter reduction was inversely associated with the degree of treatment response, as measured by the improvement in positive and negative symptoms after one week of treatment.

As has been noted above, patients that do not respond to conventional antipsychotics can benefit from the treatment with atypical antipsychotics. Only one study up to date has examined the predictive validity of structural alterations

for the atypical antipsychotics response. Friedman and colleagues (1991) compared patients who were non-responders, moderate responders, and good responders to atypical drug *clozapine*, as measured by the change in Brief Psychiatric Rating Scale (BPRS) scores after 6 weeks of treatment, on prefrontal sulcal prominence (PSP), and found a linear trend for PCP, with non-responders having highest, moderate responders an intermediate degree, and good responders the least PSP. The degree of PCP was also a significant predictor of treatment response at 6 weeks as assessed by multiple linear regression, suggesting that the effect of *clozapine* on psychopathology is associated with prefrontal structural integrity.

To the present date, no studies have assessed the validity of structural alterations in predicting the degree of cognitive improvement with atypical antipsychotic treatment. As has been discussed in *Chapter 2*, cognitive deficits are better predictors of functional outcome in schizophrenia than psychopathology. The identification of cognitive response predictors is therefore an important practical issue in schizophrenia. From a broader prospective, identifying structural markers of drug response can lead to better sub-typing of schizophrenia. As has been discussed in *Chapter 1*, schizophrenia is heterogeneous, and the work is still ongoing in defining different sub-types with greater precision for the purposes of diagnosis, treatment and research. In view of controversy surrounding the sub-typing of schizophrenia and schizophrenia diagnosis *per se*, one of the approaches to sub-typing schizophrenia might be on the basis of pathophysiology. Such pathophysiological variables as neuroanatomical abnormalities and treatment response might potentially provide a framework for categorising schizophrenia and determining its subtypes, resulting in greater reliability and validity of the diagnosis, which is necessary for the success of treatment and research.

CHAPTER 4. AIMS AND OBJECTIVES

In this chapter, the broad outline of aims and objectives will be given first, followed by the more detailed presentation of the plan of investigation and hypotheses of the experimental studies.

4.1. Aims and Objectives

The pioneering scientists of schizophrenia Kraepelin and Bleuler both believed it to be a brain disease, with its behavioural and cognitive features being manifestations of brain pathology (Chapter 2: General Introduction). Since the advent of imaging techniques it became well established that schizophrenia patients have subtle but wide-spread pattern of structural alterations (Chapter 2: Structural alterations), some of which appear to relate to cognitive (dys)function (Chapter 2: Structure/Cognition Relationships). Cognitive (dys)function, in its turn, has been shown to be of primary importance for the functional outcome (Chapter 2: Cognitive deficits), and is rapidly taking over the symptomatology as the primary target for treatment. Novel or atypical antipsychotic drugs show promise in ameliorating cognitive dysfunction, becoming the first treatment choice in first episode psychotic patients as well as chronic patients non-responsive to conventional antipsychotics (Chapter 3). The superior cognitive efficacy of atypical antipsychotics is presumed to rise due to their simultaneous action on dopaminergic and serotonergic receptors (Chapter 3). Currently, it is unclear whether structural alterations play a role in predicting response to treatment with atypical antipsychotics in terms of cognitive functioning (Chapter 3). Historically, the main approach to the study of structural alterations was the region of interest method. Being an extremely labour intensive and time consuming technique, its application precludes the identification of the comprehensive pattern of structural alterations in any given sample. With the advent of automatic processing techniques, Voxel Based Morphometry (VBM) is

gaining the momentum, primarily due to its power to map the pattern of structural alterations comprehensively by examining between group differences on a voxel-by-voxel basis throughout the entire brain, cortically and sub-cortically.

The main aims of the present investigations are: (i) to utilise this novel method for the identification of structural alterations in schizophrenia patients; (ii) to investigate the relationship of the identified global and local structural alterations to cognitive deficits most characteristic of schizophrenia; and (iii) to explore the predictive validity of structural alterations for treatment response to atypical antipsychotics in terms of cognitive improvement.

4.2. Plan of Investigation

The thesis contains four experimental chapters:
Study 1 (Chapter 5): Structural Alterations
Study 2 (Chapter 6): Cognitive Deficits
Study 3 (Chapter 7): Relationship between Structural Alterations and Cognitive Deficits
Study 4 (Chapter 8): Structural Alterations as Predictors of Treatment Response.

A sample of patients conforming to the DSM-IV diagnosis of schizophrenia and schizophrenia spectrum disorders was recruited for the investigation of structural alterations (Study 1), cognitive deficits (Study 2) and their inter-relationships (Study 3). All, but four, patients were stable on neuroleptic medication. A sub-group of these patients was subsequently switched to atypical medications, quetiapine, risperidone, or olanzapine, and re-assessed on clinical and neuropsychological measures after 6 weeks of treatment. This sub-sample constitutes the experimental group of Study 4.

PART II

STUDY 1: STRUCTURAL ALTERATIONS IN SCHIZOPHRENIA

STUDY 2: COGNITIVE DEFICITS IN SCHIZOPHRENIA

STUDY 3: RELATIONSHIPS BETWEEN STRUCTURAL ALTERATIONS AND COGNITIVE DEFICITS

STUDY 4: STRUCTURAL ATLERATIONS AS PREDICTORS OF TREATMENT RESPONSE

CHAPTER 5. STRUCTURAL ALTERATIONS IN SCHIZOPHRENIA: A VOXEL-BASED MORPHOMETRY STUDY

5.1. Introduction

Earlier efforts to identify brain abnormalities in post-mortem studies of schizophrenia patients led to conflicting findings and were flawed by irresolvable methodological issues (Plum, 1972). As a result, the idea of identifying brain neuropathology in schizophrenia was abandoned by the mid-1970s. Since the finding of lateral ventricular enlargement in schizophrenia by Johnstone and colleagues in 1976 with the help of CT, and subsequent multiple replications of this finding by CT and later by MRI studies (e.g. reviews by Shelton and Weinberger, 1986; Buckley, 1998), there was a resurge of interest in identifying neuroanatomical pathology in schizophrenia.

There is currently a substantial body of evidence to reaffirm the initial proposals by Kraepelin and Bleuler that schizophrenia involves brain pathology. However, the understanding of the nature of this pathology has shifted in recent decades. Whereas the initial search was directed towards identifying gross circumscribed lesions, perhaps in the frontal and/or temporal lobes, as originally hypothesised by Kraepelin (1919), it is becoming increasingly clear that schizophrenia is more likely to be characterised by subtle and diffuse alterations in neuronal circuitry, both cortically and sub-cortically.

The Gold Standard of brain volumetry, ROI method, was extensively applied to the study of structural pathology in schizophrenia (most recent review by Shenton et al., 2001 includes 193 peer reviewed studies published between 1988 and 2000), resulting in the implication of almost all cortical and sub-cortical structures. However, it must be emphasised, that this of course does not imply that any given individual or sample of schizophrenia patients bears all or even some of these alterations. This brings to the forefront the most serious limitation

of ROI method – being extremely laborious and time consuming it inhibits the identification of the pattern of structural alterations *comprehensively* in any given sample of patients.

The improved resolution of structural MRI scans and the development of sophisticated image processing tools have led to the emergence of automatic morphometric techniques. Amongst the most widely used are voxel-based morphometry (VBM), allowing a voxel-wise comparison of spatially normalised images; deformation-based morphometry (DBM), allowing the identification of differences in relative positions of brain structures; and tensor-based morphometry (TBM), allowing the detection of local shape differences. The discussion will be limited to a VBM approach for the present purposes.

Generally, VBM refers to a class of techniques that are applied to some scalar function of the spatially normalised (i.e. transformed into the same stereotactic space) images (whereas DBM and TBM are applied to the information coded in the deformation field obtained when spatially normalising an image in non-linear fashion). The most commonly used VBM technique involving statistical comparisons of tissue partitions (e.g. grey or white matter) has been described by Ashburner and Friston (2000) and is implemented in SPM software developed by Karl Friston and colleagues at the Wellcome Department of Institute of Neurology, London (http://www.fil.ion.ucl.ac.uk/spm/). The SPM software is a suite of MatLab (Matrix Laboratory, MathWorks, Natick, MA) functions and subroutines implementing Statistical Parametric Mapping, based on General Linear Model. SPM was originally written to organise and interpret functional neuroimaging data. The latest version of the SPM software at the time of the data analysis for the present thesis was SPM99. Therefore, the VBM approach described in this thesis refers to the VBM as implemented in SPM99.

Since the pioneering study by Wright and colleagues (1995), VBM is more and more widely applied in schizophrenia research, as well as in the study of brain pathology in other psychiatric and neurological conditions with promising results for its power to characterise and quantify local alterations in brain tissue availability with high spatial precision. From the very beginning, application of the VBM method revealed new areas of altered brain tissue, such as insula, that have previously received no attention from schizophrenia researchers due to the aforementioned limitations of the ROI approach.

As has been discussed in chapter 2, the VBM method allows identification of two indices of brain tissue alteration: *concentration* and *volume*. (Some researchers use the term 'density' instead of 'concentration'. However, the term 'density' is misleading in the VBM context, since it does not imply the same as when it is used in cytoarchitectonic studies, namely the density of neurones in neuropil. Therefore, the term 'concentration' will be used throughout the thesis to avoid this misleading connotation.)

To understand the difference between these tissue indices, one needs to consider what is involved in pre-processing of the images for VBM analysis. In its simplest, pre-processing requires three steps. First, the whole brain images are spatially normalised to the same stereotactic space by registering them to the same whole brain template, by minimizing the residual sum of squared differences between the images and the template. This is achieved using 12-parameter affine (linear) transformation (Ashburner et al., 1997) to correct for differences in brain size and orientation, followed by the non-linear transformation using a set of cosine basis functions to correct for differences in global brain shape (Ashburner and Friston, 1999). It should be noted that spatial normalisation does not attempt to match all brain features exactly. If the spatial normalisation was perfect, then all the images would be identical and no differences would be detected. Instead, spatial normalisation corrects for global brain shape differences, with VBM analysis directed towards identification of local scale differences over and above global shape variations. Second, the normalised images are segmented into grey matter, white matter, cerebrospinal fluid (CSF), and three other background classes by using a-priori classification for each voxel via registering a brain image to prior probability maps of grey matter, white matter and CSF, and applying mixture model cluster analysis technique (Ashburner and Friston, 1997) to classify the voxels into different tissue types. Finally, the segmented images are smoothed by convolving with an isotropic Gaussian kernel, usually of the size 12-mm full width at half maximum (FWHM). This last step is performed i) to make the data conform to the Gaussian field model, underlying the statistical inferences implemented in SPM99; ii) to render the data more normally distributed to ensure the validity of the parametric tests employed by SPM99; and iii) to reduce the effects of individual variation in sulcal/gyral anatomy (Ashburner and Friston, 2000). The smoothing also makes the subsequent voxel-wise analysis comparable to ROI approach, since the resulting intensity in each voxel of smoothed tissue segment is a locally weighted average of tissue availability from a region of surrounding voxels (Ashburner and Friston, 2000). The size of the region is defined by the size of the smoothing

kernel. Because of the non-linear transformation during spatial normalisation, the volumes of some brain regions will grow (i.e. new voxels will be added), whereas others will shrink (i.e. some voxels will be removed) in order to compensate for differences in brain shape between the individual image and the template. However, a relative amount of a certain tissue type to other tissue types in the normalised image will remain unchanged, since all tissue types will go through the same transformation. Consequently, a comparison of the resulting brain tissue segments with VBM will show the differences in the relative amount or *concentration* of a tissue type, i.e. the proportion of a tissue type relative to other tissue types within a region. In order to preserve the original amount of a tissue type within each structure, a further processing step was introduced, which involves the multiplication of the normalised tissue segment by the Jacobian determinants of the deformation field containing the information about image transformations during spatial normalisation. This procedure has the effect of preserving the total amount of a tissue signal in the normalised image (Goldszal et al., 1998). With this adjustment for volume change, VBM compares the absolute amount or *volume* of a tissue type in each region between groups of subjects (Ashburner and Friston, 2000).

Two formal protocols for pre-processing structural images have been described and applied in peer-reviewed publications: so called *standard* and *optimised.* The standard protocol, as originally introduced by Ashburner and Friston (2000), has been described in the previous paragraph and involves spatial normalisation, segmentation, and smoothing for the comparison of tissue concentration; plus modulation (i.e. multiplication with the Jacobian determinants), which is performed prior to smoothing, for the comparisons of tissue volumes.

The optimised protocol has been devised and validated more recently by Good et al. (2001). The main theoretical and practical underpinning of the optimised procedure proposed by Good and colleagues is that the spatial normalisation is improved by matching grey matter to grey matter prior probability template, due to the exclusion of voxels representing non-brain tissues (e.g. skull, dura matter) from the estimation of the spatial warps, which have an influence when matching whole head images to a whole head template. The low frequency basis functions employed during spatial normalisation are not good at modelling high frequency variability in skull thickness, head shape, etc. Another component of the optimised procedure is that it incorporates a few automated morphological operations at different stages of pre-processing to remove non-brain tissue that otherwise gets misclassified as grey matter. The complete optimised procedure

will be described in the Method section. For the purposes of the introduction, it suffices to say that it involves many more pre-processing steps, which makes it substantially more time consuming and computer intensive.

The standard VBM technique has been validated with ROI measurements (e.g. Vharga-Khadem et al., 1998; Job et al., 2002; Maguire et al., 2003; Saldago-Pineda et al., 2003), as well as with the phantom-lesion detection approach (e.g. Wright et al., 1999). The optimised VBM technique has been validated with an independent automated segmentation technique and ROI measurements in groups of elderly healthy subjects and patients with Alzheimer's disease and semantic dementia (Good et al., 2001).

Although theoretically, optimised protocol should yield superior segmentation of the brain into its constituting tissue types, i.e. grey, white, and CSF, it has not been tested directly in a clinical population whether optimised protocol presents an advantage over more concise and hence less time consuming standard protocol. Therefore, the aims of this study were twofold:

1) To identify a pattern of structural alterations in schizophrenia population using VBM method.
2) To compare standard and optimised VBM protocols in schizophrenia population in terms of tissue segmentation accuracy.

It was hypothesised:

1) Based on the results of the previous research, with both ROI and VBM approaches that have been outlined in Chapter 2, patients with schizophrenia would have global (i.e. whole brain and grey matter) as well as regional structural volume alterations. The local alterations were expected in the areas that are most consistently found in the ROI and VBM studies (Chapter 2: Structural Alterations), and have been implicated most strongly in the pathophysiology of schizophrenia (Chapter 2: Relationship between structural alterations and cognitive deficits), including:

Grey matter volume reduction of:

- *Prefrontal cortex* as has been observed by ROI studies, localised to the *Inferior Frontal Gyrus* (IFG) by previous VBM studies;
- *Superior Temporal Gyrus* (STG), as has been observed in all ROI studies measuring grey matter volume of this structure as well as more recently by some (but not all) VBM studies;

- *Hippocampal complex*, as has been observed in 74 % of the ROI studies and some (but not all) VBM studies;

Grey matter volume increases of:

- *Basal Ganglia* structures, including caudate and putamen, possibly due to neuroleptic medication exposure.

Further alterations were expected in cortical regions understudied with ROI approach, such as parietal and occipital lobes. Global white matter was predicted to be unchanged in patients, since total white matter volume reduction is not found as reliability as that of total grey matter volume (review, Lawrie and Abukmeil, 1998). No predictions were made as to local white matter availability.

2) An optimised protocol would result in superior tissue segmentation compared with standard protocol.

The absolute local tissue alterations were of interest to make the findings of this study directly comparable with the existing literature using ROI method. Therefore, the volume rather than concentration of grey and white matter was compared between patients and healthy individuals.

A further aim of the study was to investigate the inter-relationships of structural volume alterations in schizophrenia patients. Although many MRI studies reported more than one morphological abnormality in schizophrenia patients as a group, little is known about the associations between the alterations in the volume of different brain regions. Previously, Wible and colleagues (1995) reported left prefrontal grey matter volume to correlate with volume reductions in the left amygdala-hippocampal complex, left STG, and left parahippocampal complex in schizophrenia patients. Correlations between these brain regions were not observed in controls. In an exploratory study of structural brain volume relationships in schizophrenia patients and normal controls using factor analysis, Tien et al. (1996) observed the disrupted relationship between dorsolateral prefrontal and superior temporal volumes in schizophrenia patients that was present in normal controls. Subsequently, Woodruff and colleagues (1997b), who investigated associations between several brain regions in male schizophrenia patients, also reported disrupted frontal-temporal volume relationship in patients relative to normal controls. Finally, Bullmore and colleagues (1998) re-assessed the data reported by Woodruff et al. (1997b) using statistical methods based on information theory and principal component analysis, and also showed reduced dependencies between frontal and temporal lobe volumes in schizophrenia.

Therefore, the present study wished to further investigate the inter-relationships between brain regions that are altered in schizophrenia patients, and compare the associations found in patients with those in controls.

Finally, structural volume alterations in patients were investigated in relation to their clinical characteristics.

5.2. Method

5.2.1. Participants

5.2.1.1. The inclusion criteria

The inclusion criteria for the patients were i) no neurological conditions; ii) no additional (to schizophrenia) diagnosis of DSM IV axis-I-disorder (First et al., 1996a); iii) no concomitant diagnosis of drug or alcohol abuse; and iv) no previous experience with the neuropsychological measures used in the study.

The inclusion criteria for healthy volunteers were i) no personal history of DSM-IV Axis I and II disorders (First et al., 1996a); ii) no familial history of psychosis (as determined by the Family Interview for Genetic Studies (FIGS), Gershon and Guroff, 1984); iii) no neurological conditions; iv) no drug or alcohol abuse; and v) no previous experience with the neuropsychological tests.

Both patients and controls had English as their first language.

5.2.1.2. Overall sample

50 in- and out- patients in the category of DSM-IV schizophrenia or schizophrenia-related disorders and 48 healthy controls, right handed, age between 18-65 years, were recruited for the investigation. Diagnoses were ascertained by experienced psychiatrists of the Section of Cognitive Psychopharmacology, Institute of Psychiatry, using the structured Clinical Interview for DSM-IV Axis I disorders Research Version (SCID-I; First et al., 1996b). All participants gave informed consent prior to the participation. Five patients were excluded: three females due to the MRI motion artefact and two males due to brain tumours as revealed upon the examination of the structural

MRI scans. Three controls were excluded due to the MRI motion artefact: two females and one male.

5.2.1.3. Final Sample

Forty five schizophrenia patients, 27 male and 18 female, and 43 healthy controls, 25 male and 18 female, have met all of the above criteria, as well as passed the stringent quality control of the MRI scans, and thus constitute the final sample (see *Table 5.1* for demographic characteristics). The groups were closely matched on sex, ethnicity and parental socio-economic status (SES). The schizophrenia patients were significantly older (Mean = 40.49, sd = 11.67, range 18-61) than the controls (Mean = 33.72, sd = 12.37, range 19-65) [p=.01]. This group difference was due to significantly older female patients (Mean=42.33, sd=12.47, range 21-61) relative to female controls (Mean=30.72, sd=12.70, range 20-65) [p=.008], which resulted from the exclusion of two younger female patients and two older female controls due to the reasons stated above. Male participants were closely age matched, with male patients having the mean age of 39.26 years (sd=11.18, range 18-61) and male controls having th mean age of 35.88 years (sd=12.28, range 19-60) [p=.304].

Parental SES is closely associated with the level of educational achievement in normal population (e.g. Okpala, Okpala, and Smith, 2001; Bradley, 2002). Individuals with schizophrenia often achieve lower level of education that would be predicted from their social class (e.g. Isohanni et al., 2001). This might be due to cognitive problems experienced very early in life (e.g. Isohanni et al., 2004). The current sample confirms this pattern. Although the patients closely matched controls on parental SES, their level of educational achievement was substantially lower (patients' mean=11.93, sd=3.08; controls' mean=16.31, sd=3.44) [p<.0001]. This was true for both male (patients' mean=12.19, sd=3.45; controls' mean=16.38, sd=3.40) [p<.0001] and female (patients' mean=11.56, sd=2.45; controls' mean=16.22, sd=3.59) [p<.0001] sub-groups.

Table 5.2 lists clinical characteristics of the patients, including the diagnosis, illness type, familial history, age of onset, age of first hospitalisation, duration of illness, number of previous episodes, and symptom ratings using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987).

TABLE 5.1. Demographic Characteristics of the Final Sample

Characteristic		**Patients (N=45)**	**Controls (N=43)**	**Statistics**
		Mean (SD) [Range]	**Mean (SD) [Range]**	
Male/Female		27/18	25/18	X^2 = .031; p=.859
Age:	Group	40.49 (11.67) [18-61]	33.72 (12.37) [19-65]	T_{86} = 2.60; p=.01
	Male	39.26 (11.18) [18-61]	35.88 (12.28) [19-60]	T_{50} = 1.039; p=.304
	Female	42.33 (12.47) [21-61]	30.72 (12.70) [20-65]	T_{34} = 2.824; p=.008
Education:	Group	11.93 (3.08) [5-22]	16.31 (3.44) [11-25]	T_{86} = -6.302; p<.0001
	Male	12.19 (3.45) [5-22]	16.38 (3.40) [11-25]	T_{50} = -4.408; p<.0001
	Female	11.56 (2.45) [7-17]	16.22 (3.59) [11-24]	T_{34} = -4.552; p<.0001
Ethnicity:	Caucasian	37	36	
	African	4	3	
	South-East Asian	2	2	X^2 = .526; p=.640
	Mixed Race	1	1	
	Other	1	1	
Parental SES:		(N=41)	(N=43)	
	Professional	5	6	
	Intermediate	13	13	
	Skilled: non-manual	1	3	X^2 = .008; p=.930
	manual	10	8	
	Semi-skilled manual	7	8	
	Unskilled manual	5	5	

TABLE 5.2. Clinical Characteristics of Patients

Characteristic	**First Episode (n=4)**	**Chronic (n=41)**	**Total (n=45)**
Diagnosis:	N/A	**Total (M/F)**	
Schizophrenia, paranoid		28 (20/8)	
Schizophrenia, undifferentiated		3 (1/2)	
Schizophrenia, residual		9 (5/4)	
Schizoaffective disorder		1(1/-)	
Family history:			
Yes		12 (10/2)	
No		28 (16/12)	
Missing data	4	1 (1/-)	
	Mean (SD) [Range]	**Mean (SD) [Range]**	**Mean (SD) [Range]**
Age at onset of first symptoms:	27.25 (4.79) [21-31]	25.15 (9.17) [15-59]	25.33 (8.85) [15-59]
Number of previous episodes:	N/A	4.41 (4.62) [1-20]	
Age at first hospitalisation:	27.25 (4.79) [21-31]	22.46 (12.21) [0-59]	22.89 (11.78) [0-59]
Previous psychiatric hospitalisations:	N/A	3.71 (4.02) [0-20]	
Duration of illness since first symptoms (years):	N/A	16.88 (11.69) [1-39]	
		N=38	**N=42**
PANSS Positive symptoms:	27.75 (2.22) [25-30]	17.11 (7.12) [7-32]	18.15 (7.50) [7-32]
PANSS Negative symptoms:	21.50 (5.07) [17-28]	17.83 (8.08) [7-52]	18.20 (7.86) [7-52]
PANSS General Psychopathology:	57.75 (5.12) [53-65]	37.27 (9.82) [13-55]	39.27 (11.25) [13-65]

All but ten patients received conventional antipsychotics, either orally or as a depot injection (chlorpromazine equivalents mean = 283.76, sd = 254.96, range 31.25-1000 mg/day). Fifteen patients were receiving adjunctive anticholinergic medication (procyclidine, mean = 5.9, sd = 2.93, range 2.5-15 mg/day).

5.2.2. MRI Data Acquisition

Structural images were acquired using a 1.5 Tesla GE NV/*i* MR Signa system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London, with routine daily quality control, using an automated procedure (Simmons et al., 1999). A high-resolution 3-D inversion recovery prepared spoiled GRASS pulse sequence was used to acquire a T1-weighted volume in the axial plane (TR=12.2 ms, TE=5.3 ms, TI=300 ms, flip angle=20°, in-plane resolution=.94 mm, matrix dimensions 256 x 256), yielding 124 contiguous slices of 1.5 mm thickness. Head movement was limited by foam padding and a restraining band across the forehead.

5.2.3. MRI Data Pre-processing

Structural images were converted into ANALYZE format (ANALYZE software, BRU, Mayo Foundation, Rochester, MN; Robb, 1990) and pre-processed using SPM99, running in MATLAB 6.1 (MathWorks, Natick, MA). A manual determination of the anterior commissure was performed for all images in preparation for the processing. Patients and controls did not differ on intra-scanner movement (rotations no larger than 1 degree or translations no greater than 1 mm), using a group (patients vs controls) x movement dimension (x, y, z, pitch, roll, yaw) ANOVA ($p<.345$). The images were then pre-processed following the standard and optimised VBM protocols.

5.2.3.1. Standard Protocol

First, images were spatially normalised to the standard SPM99 T1 whole brain template. The standard SPM99 whole brain template for T1-weighted images is an average of 152 MRI scans of young healthy brains from the Montreal Neurological Institute, which has been adopted as an international standard by the International Consortium of Brain Mapping and is known as ICBM152. The images were normalised using 12-parameter linear transformation followed by non-linear iterations using 7 x 8 x 7 basis functions as integrated in SPM99. The

normalised images were written down with 1x1x1 mm voxel size to reduce the partial volume effect aiding the segmentation. Second, the normalised images were segmented into grey matter, white matter, CSF and non-brain tissue using prior probability maps of different tissue types inherent to SPM99. Third, the segmented images were modulated by multiplying with Jacobian determinants of the deformation fields to correct for volume changes introduced during non-linear transform. Finally, the images were smoothed with 12-mm FWHM isotropic Gaussian kernel. The width of the smoothing kernel determines the scale at which morphological changes are most sensitively detected, since smoothing creates a local weighted average of the surrounding pixels. The use of 12-mm kernel was recommended by Ashburner and Friston (2000) to insure the validity of the following statistical tests and has been accepted as a 'Gold Standard' by researchers. Smoothing kernels of smaller sizes might not be sufficient to render the data normally distributed, making analyses susceptible to false-positive errors.

5.2.3.2. Optimised Protocol

The original structural images were re-processed following the optimised protocol devised by Good et al. (2001).

Creation of Customised Templates

As the first step, study specific (customised) whole brain template and prior probability maps were created to improve the spatial normalisation. Since the standard SPM99 templates were created from the images of the young healthy individuals, they might not be suitable for normalising brains of the population with deviant brain features, such as enlarged ventricles, biasing their normalisation. Customised whole brain templates as well as grey-, white- matter, and CSF prior probability maps were therefore created from the images 40 patients (25 male and 15 female) and 40 controls (25 male and 15 female) of the present sample matched as closely as possible on demographic variables.

For the whole brain template, the images were spatially normalised to T1-weighted template (ICBM 152 standard, inherent to SPM99), using 12-parameter affine transformation only (Ashburner et al., 1997); smoothed with 8 mm full width half maximum (FWHM) isotropic Gaussian kernel; and averaged. For customised probability maps, images were segmented into grey-, white- matter, and CSF compartments using grey-, white- matter, and CSF probability maps

inherent to SPM99. The resultant tissue segments were automatically cleaned to remove non-brain tissue; smoothed with 8-mm FWHM isotropic Gaussian kernel; normalised using customised whole brain template with 12-parameter affine transformation; and finally averaged to derive grey-, white- matter, and CSF probability maps. Templates were created with 1x1x1 mm voxel size to reduce the partial volume problem and to ensure optimal tissue segmentation.

Deriving and Applying Optimised Normalisation Parameters

The first step involved a segmentation of the original images in native space, registering to the customised tissue probability maps and correcting for image inhomogeneity, followed by the automatic brain extraction and cleaning procedure to remove non-brain tissue. Second step entailed spatial normalisation of the original images to the customised whole brain template using 12-parameter linear and 7 x 8 x 7 discrete cosine transform basis function non-linear transformations (Ashburner and Friston, 1999), with parameters determined from the images derived from the first step; and resliced to 1x1x1 mm voxel size to yield more accurate subsequent tissue segmentation. The spatially normalised images were then segmented into three tissue compartments, using the customised grey-, white- matter, and CSF templates. Brain extraction and cleaning procedures were re-applied to the segmented normalised grey matter images to further remove extraneous brain tissue. The cleaned grey matter images were modulated, i.e. the voxel values of each segment were multiplied by the Jacobian determinants of the deformation matrix derived during the spatial normalisation step. The modulation 'restores' the original volume of each grey matter segment, as the volume of some brain regions may shrink or expand as a result of non-linear spatial normalisation. Finally, grey and white matter segments were smoothed using 12-mm FWHM isotropic Gaussian kernel.

5.2.4. Data Analysis

5.2.4.1. VBM model specification and parameter estimation

The model and parameters for SPM voxel-wise comparisons of the images processed with standard and optimised protocols were identical.

First, global tissue availability indices, global grey-, white- matter, and whole brain volumes (global grey + global white) were calculated using an integral

function (SPM list archives, http://www.jiscmail.ac.uk/lists/spm.html) applied to the original structural images. The values (in litres) for total grey and white matter volumes were used in voxel-wise comparisons to control for individual variations in tissue availability. The correction for differences in total tissue volumes decreases the rate of false positive errors in VBM (Ashburner and Friston, 2000). Further, the total volumes were entered into SPSS version 10 and compared using analysis of covariance (ANCOVA), controlling for age and sex for their known influence on brain morphology (Coffey et al., 1998), to investigate whether there were alterations in global tissue volumes in patients.

To compare the groups on the regional volumes of grey and white matter voxel-by-voxel, the grey/white matter segments of patients and controls were proportionally scaled to total grey/white matter volume with the global mean of 100, adjusting for the confounding effects of age and sex. Therefore, each region of group difference represents the difference in the proportion of total grey/white matter volume in that region between the groups.

The predicted values (y' adjusted = y' fitted + error) for the percentage of total grey/white matter volume at the maxima voxel of all the regions of between-group differences were extracted for each participant for the analyses of the inter-relationships between altered regions, as well as their relationship with clinical variables in SPSS.

5.2.4.2. Statistical comparisons

For the statistical comparisons of regional volumetric differences between the groups normalising for whole grey/white matter volumes and covarying for the effects of age and sex, SPM proceeds through the following steps:

i) performs a statistical analysis for each voxel independently;

ii) calculates a *t* statistic from the results of this analysis for each voxel;

iii) calculates a z score equivalent for the t statistic;

iv) estimates a *p* value for a *t* statistic at each voxel independently;

v) estimates a corrected *p* value adjusted for multiple comparisons performed for the entire brain.

For the steps i) to iv), SPM uses General Linear Model (GLM), where

- a voxel value for each scan is an *observation*;
- data for all the scans for one voxel (i.e. all the observations) is a *dependent variable* (a response);

- a diagnosis is an *independent variable* (a predictor), covariate for the effects of age and sex.

To solve the multiple comparison problem (step v), SPM uses random field theory (RFT). (Since the brain voxels are spatially correlated, Bonferroni correction is too conservative as it assumes independent tests.) The RFT correction is based on the number of *resels* in the image and *Euler characteristic* (EC) of the image. A resel is a "resolution element" and is defined as a block of pixels of the same size. The size of the pixels in its turn is determined by FWHM of the image smoothness. As the images were smoothed with 12mm FWHM kernel, one resel is a 12 x 12 pixel block. The number of resels is conceptually similar to the number of independent observations in the image, but it is not equivalent to it. The EC of an image is a property of the image after it has been thresholded, which means that all pixels with z scores below or equal to the threshold value will be set to zero and all pixels with z scores above the threshold value will be set to one. The RFT correction proceeds through determining the number of resels in the image, uses the resel count to work out the expected EC of the image at various thresholds, and finally calculates the alpha (the rate of false positives) for the results observed at the set threshold from the expected ECs.

For all comparisons in SPM99, the threshold for statistical parametric maps was set at $T = 3.20$, $p<.001$ uncorrected. The spatial extent threshold was set at 25 contiguous voxels, since clusters of smaller size are more likely to arise by chance (Wilke et al., 2001). The results were considered to be statistically significant at $p<.05$ voxel level corrected for multiple comparisons throughout the entire brain. For the predicted regions (see Introduction), small volume corrections (SVC) were used when adjusting for multiple comparisons to reduce the search-volume to the regions of interest. Further, since the multiple comparisons correction procedure in SPM99, which was originally designed for the analysis of functional data, is overly strict when applied to the structural data (Sowell et al., 1999), the unpredicted regions of differences that did not reach 5% level after multiple comparisons correction but exceeded $T = 4.00$ ($p<.00001$ uncorrected) were considered to be a trend and, therefore, of interest for the investigation of structure/neurocognition associations of Study 3.

SPM99 displays the results as a statistical parametric map and uses Talairach and Tournoux system of coordinates (i.e. $x = 0$, $y = 0$, $z = 0$ at the anterior commissure, and with the anterior / posterior commissural line defining the plane

where z = 0). Since the MNI templates in SPM99 are larger (i.e. higher, deeper and longer) than the brain pictured in the Talairach and Tournoux atlas (1988), with differences at maximum in the order of 10mm, MNI x y z coordinates of significant and of interest voxels were converted to Talaraich and Tournoux space using a non-linear transform (Brett, 1999). The voxel locations were then identified using the Talairach and Tournoux atlas (1988) and the *Talairach Daemon* software (Lancaster et al., 2000).

5.3. Results

5.3.1. Global tissue alterations

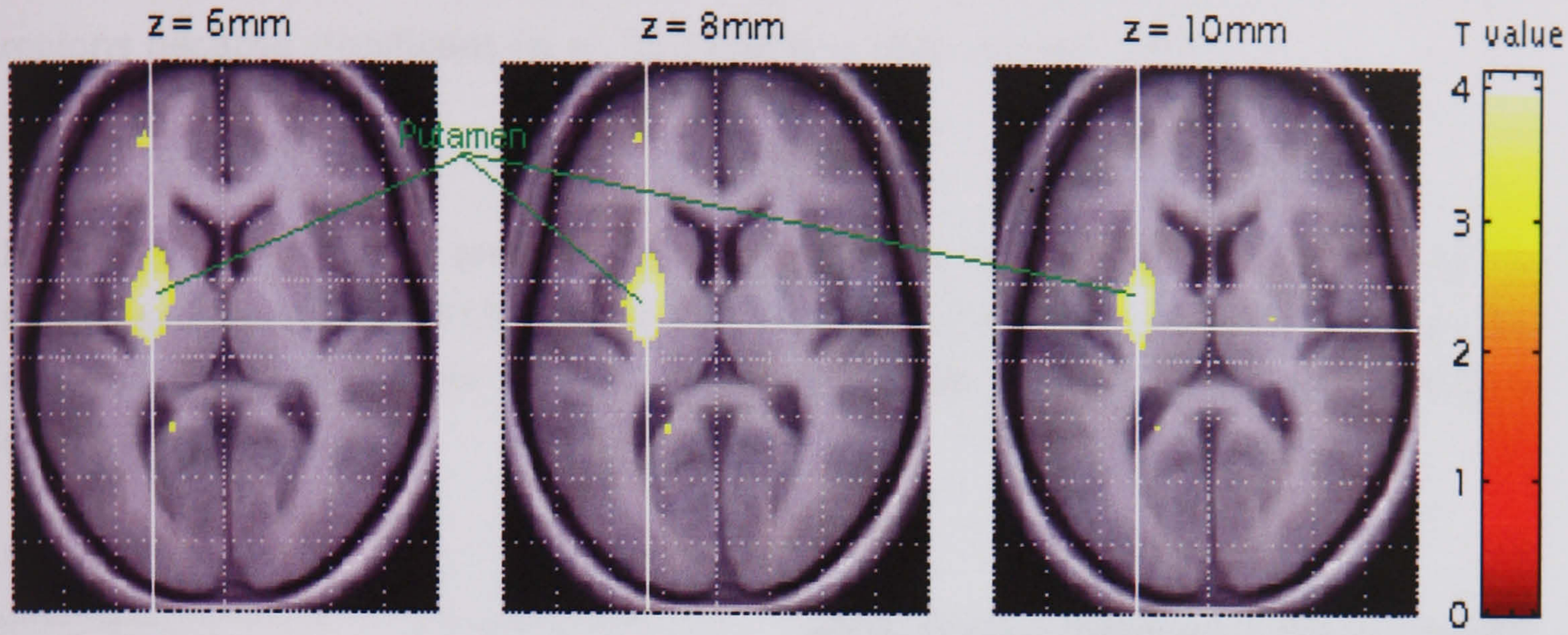
Patients had decreased global grey matter, white matter, and whole brain volumes (in litres). The grey matter volume was reduced by 9% (patients' mean = .659, sd = .007; controls' mean = .725, sd = .008) [$F_{(1,84)}$ = 13.956, p<.0001], beyond the significant confounding effects of age [p=.001] and sex [p<.0001]. The white matter volume was reduced by 7% (patients' mean = .384, sd = .006; controls' mean = .414, sd = .005) [$F_{(1,84)}$ = 8.554, p = .004], beyond the significant effect of sex [p < .0001] (but not age [p = .234]). The whole brain volume was reduced by 9.5% (patients' mean = 1.043, sd = .118; controls' mean = 1.138, sd = .129) [$F_{(1,84)}$ = 13.498, p <.0001], beyond the significant effects of sex [p < .0001] and a trend effect of age [p = .065].

5.3.2. Local Tissue Alteration

5.3.2.1. Standard Protocol

The pre-processing with the standard protocol resulted in the mis-registration of the images and a faulty segmentation, such that at least some of the grey matter voxels were misclassified as white matter. This became apparent when the white matter segments of patients and controls were compared. The SPM revealed a cluster of increased volume with the voxel of the maximum difference at x = -26, y = -14, z = 8. When the SPM was overlaid on the average image of patient group, the cluster fell onto the putamen (*Figure 5.1.*).

FIGURE 5.1. The cluster of presumably increased white matter (maxima voxel: x = -26, y = -14, z = 8) in schizophrenia patients overlaid on mean patient structural image, demonstrating misregistration with the standard VBM protocol



5.3.2.2. Optimised Protocol

The optimised pre-processing appeared to have yielded accurate normalisation and segmentation. The results of the optimised protocol were therefore treated as final and are reported in this chapter (see Table 5.1.).

TABLE 5.3. Structural Alterations in Schizophrenia Patients

Brain Region	**Brodmann Area**	**Cluster size (# voxels)**	**Maxima voxel x, y, z**	**T value**	**p uncorrected**	**p corrected**
Inferior Frontal Gyrus	BA 45/47	3947	-33 28 -8	4.72	<.0001	.025
Lingual Gyrus	BA 17	4213	-22 –89 -6	4.34	<.0001	.05
Superior Temporal	BA 38	4290	-36 22 -31	4.27	<.0001	.105
Gyrus			-50 14 -34	4.08	<.0001	.179
Putamen	-	637	-29 –7 9	4.19	<.0001	.132
Precuneus	BA 7	1052	-13 –76 35	4.05	<.0001	.157
Superior Fasciculus Longitudinalis	-	3578	-28 –38 26	4.18	<.0001	.126
Occipital White Matter	-	851	-15 –86 -1	4.07	<.0001	.172

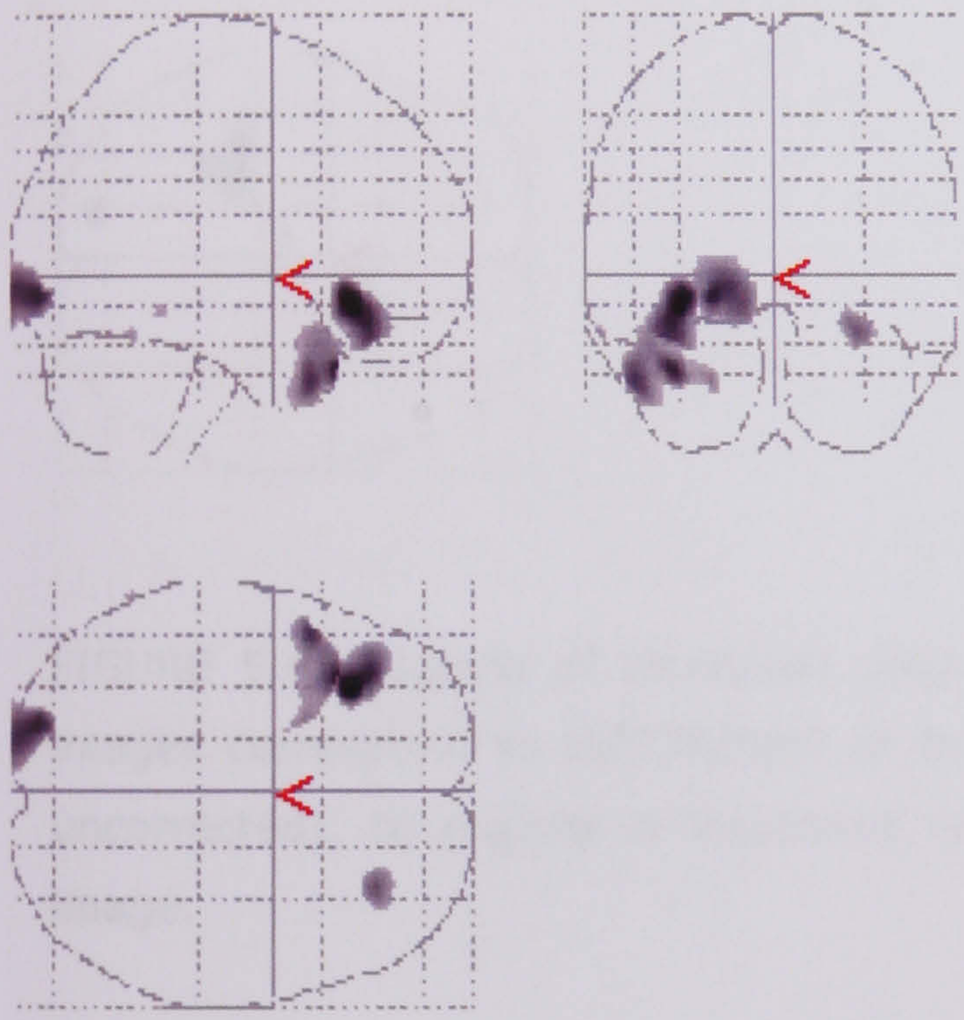
Reductions

The grey matter volume was significantly reduced in two left hemisphere regions: the inferior frontal gyrus [IFG, BA 45/47, centred at the voxel x = -33, y = 27, z = -8, $t_{(84)}$ = 4.72, p = .025], and the lingual gyrus [LG, BA 17, x = -22, y = -86, z = -9, $t_{(84)}$ = 4.34, p = .05]. In addition, two voxels in the left anterior superior temporal gyrus (STG) showed trend significance [BA 38, voxel 1: x = -36, y = 20, z = -27, $t_{(84)}$ = 4.27, p = .105, and voxel 2: x = -50, y = 12, z = -

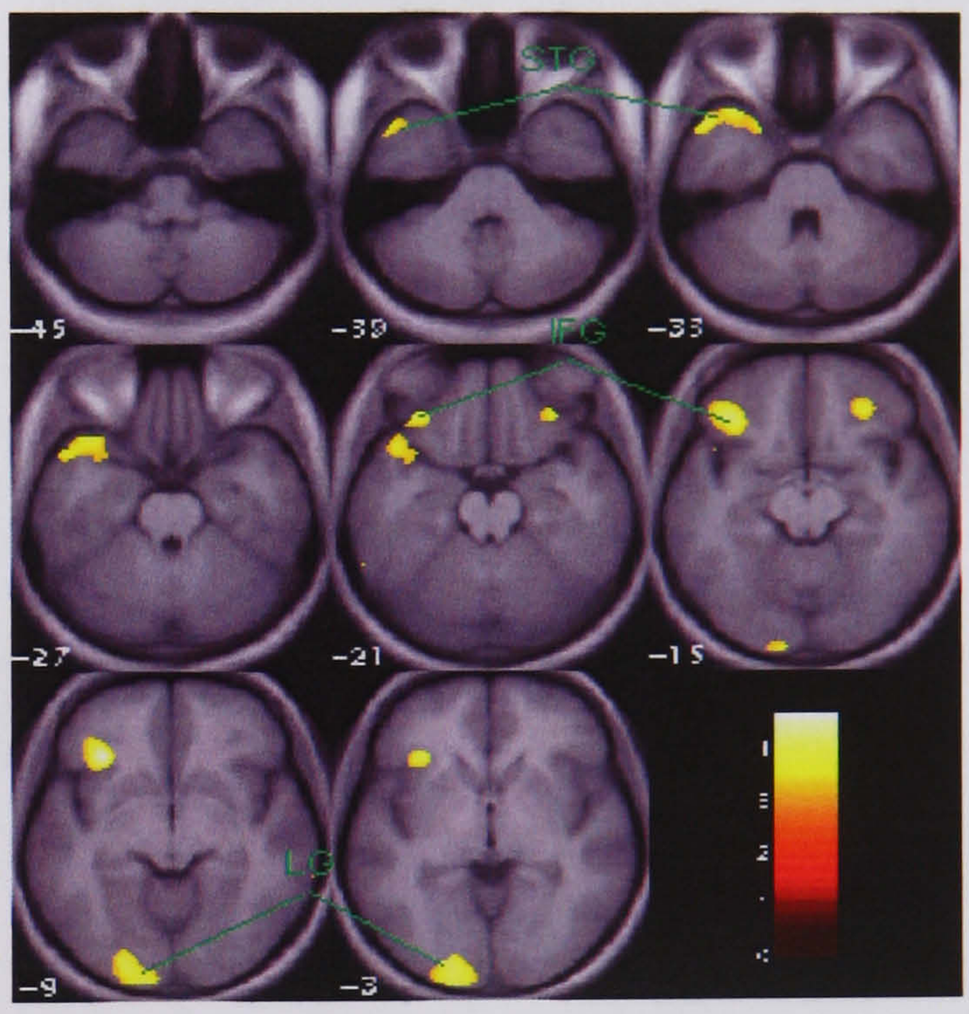
29, $t_{(84)} = 4.08$, $p = .179$] after correction for multiple comparisons through the entire brain (see *Figure 5.2*). After the SVC was applied to STG, as it was one of the hypothesised regions, restricting the search volume to the temporal lobe (box with the dimensions: x = 50mm, y = 60mm, z = 40mm), the difference in STG regions became significant [p = .012 and p = .021 respectively].

FIGURE 5.2. Regions of grey matter volume reductions in patients (LEFT/RIGHT of the images correspond to LEFT/RIGHT of the brain): a) statistical parametric map (p<.001 uncorrected); b) regions of reduced volume in patients overlaid on the mean image of controls.

a)



b)

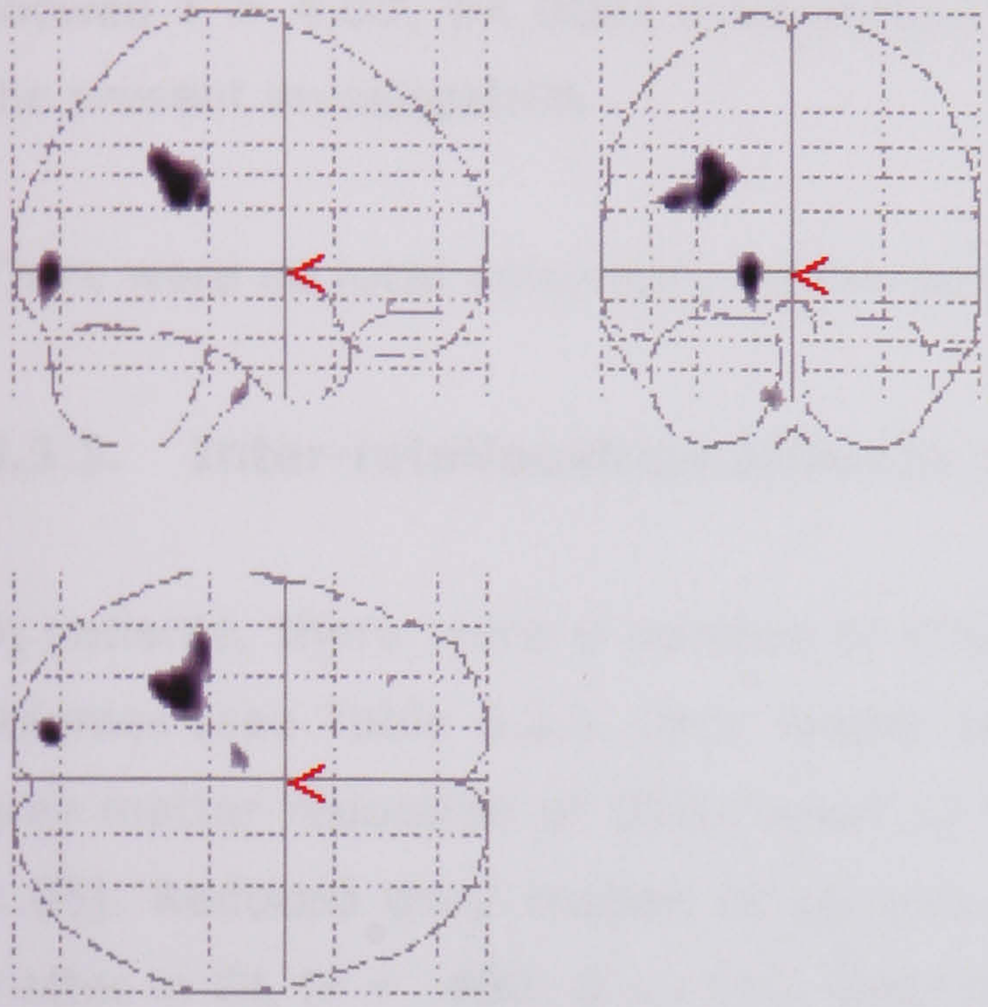


ABBREVIATIONS: IFG = Inferior Frontal Gyrus; LG = Lingual Gyrus; STG = Superior Temporal Gyrus.

The white matter volume was reduced at a trend level in the posterior lobe (in the region of the superior fasciculus longitudinalis) [SFL, x = -28, y = -36, z = 26, $t_{(84)} = 4.18$, $p = .126$], and occipital lobe (OL) in the primary visual cortex [x = -15, y = -86, z = -1, $t_{(84)} = 4.07$, $p = .172$] (see *Figure 5.3*).

FIGURE 5.3. Regions of reduced white matter volume in patients (LEFT/RIGHT of the images correspond to LEFT/RIGHT of the brain): a) statistical parametric map ($p<.001$ uncorrected); b) regions of increased volume in patients overlaid on the patients' mean image.

a)



b)

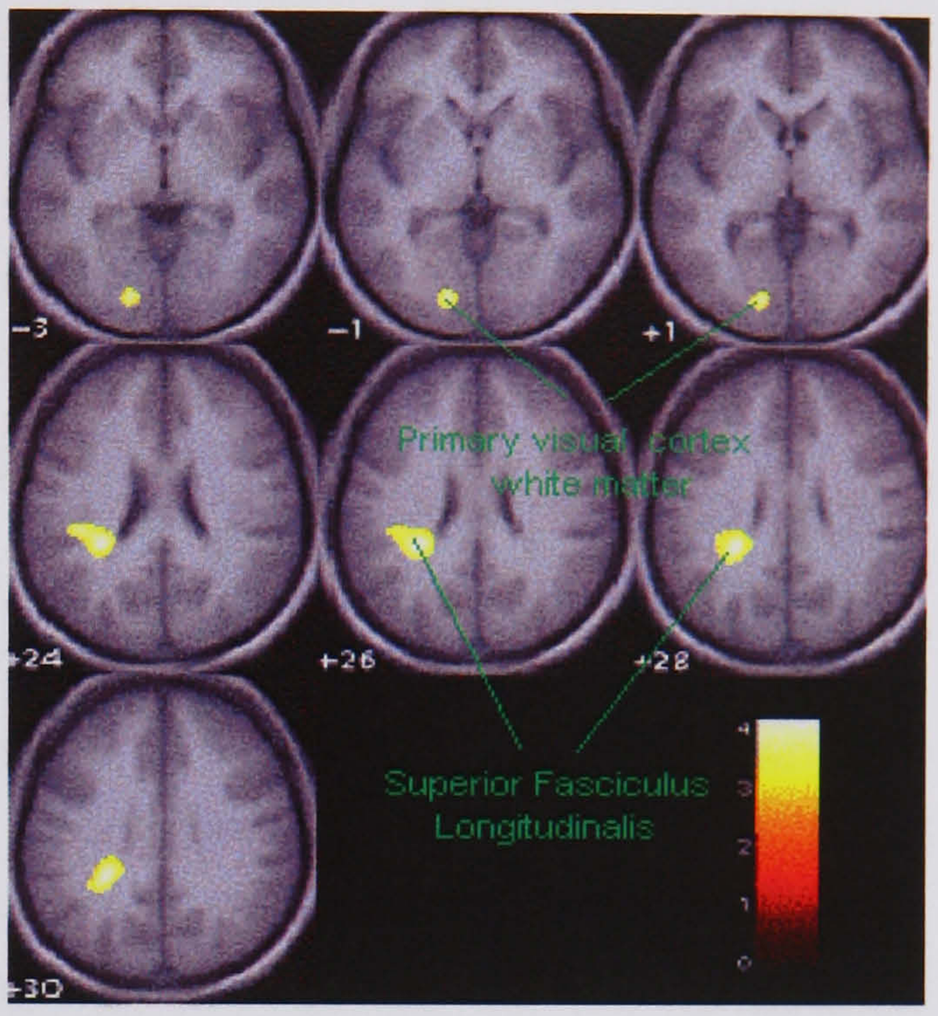
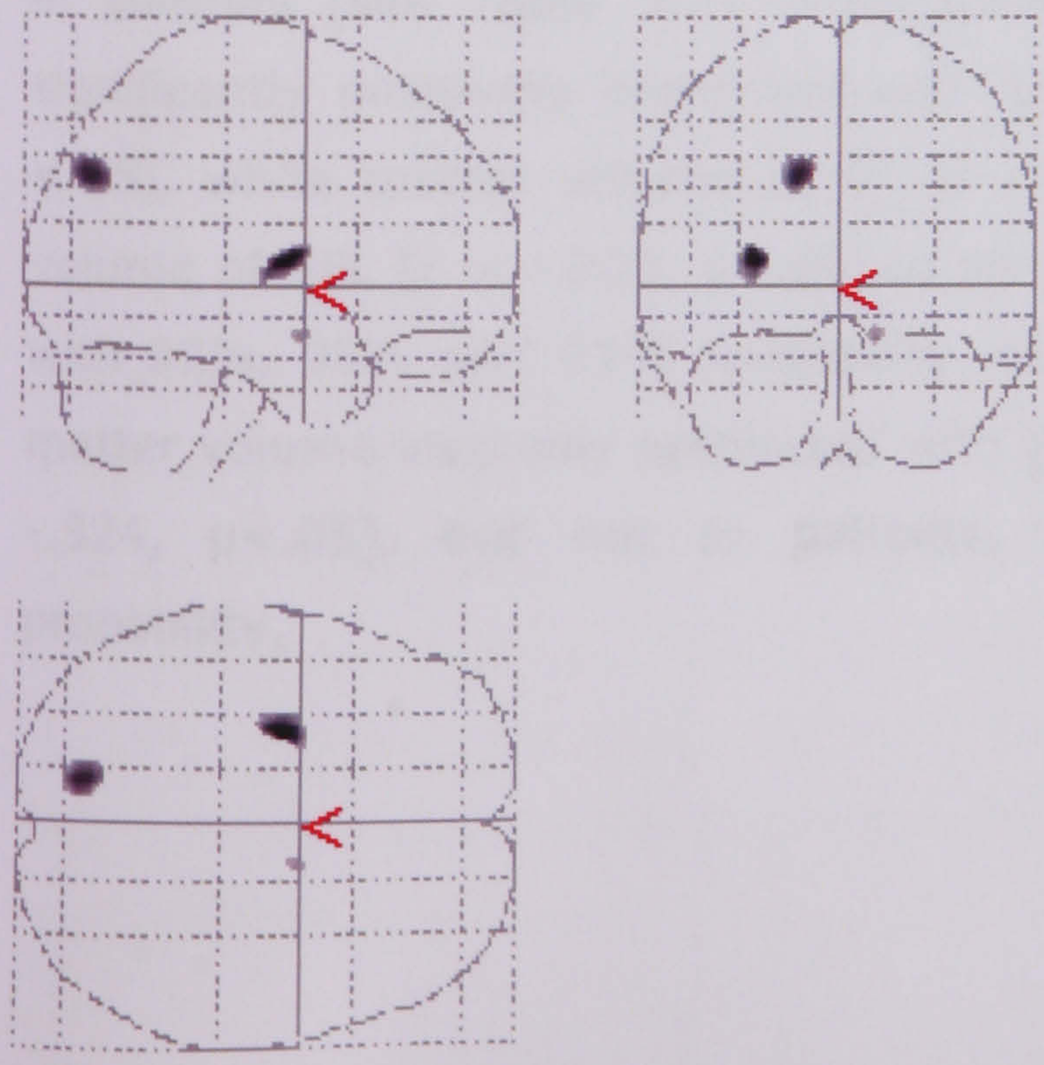


FIGURE 5.4. Regions of increased grey matter volume in patients (LEFT/RIGHT of the images correspond to LEFT/RIGHT of the brain) : a) statistical parametric map ($p<.001$ uncorrected); b) regions of increased volume in patients overlaid on the patients' mean image.

a)



b)

Increases

Patients had more grey matter relative to controls in two left-hemispheric regions (see *Figure 5.4)*: posterior putamen [x = -29, y = -6, z = 9, $t_{(84)}$ = 4.19, p = .029 after the SVC with the search volume restricted to basal ganglia (sphere of 40 mm radius) and the precuneus [BA 7, x = -13, y = -72, z = 35, $t_{(84)}$ = 4.05, p = .157] which, although not significant after correcting for multiple comparisons, showed T > 4.00, p<.0001 uncorrected, and thus was considered of interest to the present investigation.

There were no local volumetric increases of the white matter.

5.3.3. Inter-relationships between Local Tissue Volumes

In patients, there were a number of inter-relationships between altered regional volumes (see Table 5.2.). Grey matter reduction of IFG was associated with the grey matter reduction of STG (voxel 1) [r = .335, p <.05] and LG [r = .344, p <.05]. Reduced grey matter of LG was associated with the reduction of white matter in OL [r = .450, p <. 01]. Grey matter reduction in two STG regions was strongly associated [r = .705, p <.001]. Grey matter increase in putamen was inversely associated with white matter reduction in SFL [r = -.483, p <. 01]. The associations between these brain regions were also present in controls; except for the inverse relationship between putamen and SFL, which was significantly stronger in patients [p = .03].

There was also attenuation or lack of associations in patients that were significant in controls (see *Table 5.2*). Particularly, grey matter volume of STG 1 was significantly positively correlated with grey matter volume of LG [r = .346, p <.05], white matter volume of OL [r =.364, p<.05], and inversely with white volume of SFL [r = -.303, p<.05] in controls, differentiating them from patients with 82%, 98% and 91% probability respectively. In addition, precuneus grey matter volume inversely correlated with SFL white matter volume in controls [r = -.324, p<.05], but not in patients, differentiating the groups with 88% probability.

TABLE 5.4. Partial *r* correlation coefficients, adjusted for age and sex, expressing the inter-relationships between regional volumes in patients and controls. The *r* coefficients in two groups are compared using Fisher *z* transformations with the p values shown in brackets.

	LG	**STG1**	**STG2**	**Pu**	**Prec**	**SFL**	**RO**
	P/C (p value)	P/C (p value)	P/C (p value)	P/C (p value)	P/C (p value)	P/C (p value)	P/C (p value)
IFG	.344*/.130 (.30)	.335*/.371* (.84)	.228/.351* (.55)	-.263/-.232 (.88)	.054/.277 (.29)	-.040/-.078 (.87)	.088/.101 (.95)
LG		.066/.346* (.18)	-.067/.139 (.35)	-.120/-.171 (.81)	.253/-.057 (.37)	.260/-.064 (.13)	.450**/.682** (.12)
STG1			.704**/.665** (.65)	-.154/-.390** (.24)	.056/.007 (.83)	.067/-.303* (.09)	.024/.364* (.02)
STG2				-.067/-.088 (.92)	-.010/.033 (.92)	-.027/-.132 (.63)	-.198/.274 (.03)
Pu					.037/.224 (.38)	-.483**/-.046 (.03)	.103/-.064 (.45)
Prec						.005/-.324* (.12)	.103/-.190 (.18)
SFL							.120/-.164 (.19)

* Significant at the 0.05 level (2-tailed)

** Significant at the 0.01 level (2-tailed)

ABBREVIATIONS: IFG = inferior frontal gyrus; LG = lingual gyrus; P/C = Patients/Controls; Prec = precuneus; Pu = putamen; STG = superior temporal gyrus; SFL = superior longitudinal fascicules.

5.3.4. Relationships between Structural Alterations and Clinical Characteristics of Patients

Significant associations between structural alterations and medical history were observed for: i) smaller LG and greater number of previous psychotic episodes [r = -.376, p<.05]; ii) smaller SFL and greater number of previous psychotic episodes [r =-.321, p<.05] and hospitalisations [r =-.323, p<.05]; and iii) larger precuneus and greater number of previous psychotic episodes [r =.444, p<.01] and hospitalisations [r =.402, p<.01](see Table 6.3.). In addition, patients with familial history of schizophrenia had significantly smaller grey matter of the anterior STG 2 than patients with no familial history [$F_{1, 36}$ = 3.696, p = .05]. Finally, since enlarged striatum has been shown to associate with neuroleptic exposure (Chakos et al., 1994), the putamen volume was investigated in relation to current neuroleptic dose, but no relationship has been found (r = -.034, p = .852). Precuneus increase was also unrelated to current neuroleptic dose (r = -.039, p =.827).

Structural alterations were also associated with psychopathology, including: i) smaller total grey matter volume and higher PANSS positive symptoms [r =-.362, p<.05]; ii) larger putamen and lower PANSS positive symptoms [r =-.510, p<.01] and general psychopathology [r =-.432, p<.01]; and iii) smaller SFL and lower PANSS general psychopathology [r =.362, p<.05] (see Table 5.3).

TABLE 5.5. Partial *r* correlation coefficients, adjusted for age and sex, between structural alterations and clinical characteristics of the schizophrenia patients

Whole brain volume	None
Total grey matter	
PANSS positive syndrome	-.362*
Total white matter	None
Inferior Frontal Gyrus, BA 47/45	None
Lingual Gyrus, BA 17	
Number of previous episodes	-.376*
Superior Temporal Gyrus 1, BA 38	None
Superior Temporal Gyrus 2, BA 38	None
Putamen	
PANSS positive syndrome	-.510**
PANSS general psychopathology	-.432*
Precuneus, BA 7	
Number of previous episodes	.444*
Number of previous hospitalisations	.402*
Superior Fasciculus Longitudinalis	
PANSS general psychopathology	.362*
Number of previous hospitalisations	-.323*
Number of previous episodes	-.321*
White matter of OL	None

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

5.4. Discussion

Towards achieving the primary aim of this investigation, i.e. identification of structural volume alterations in schizophrenia patients throughout the brain, the structural data were initially processed according to the standard VBM protocol. However, it has resulted in the segmentation fault, such that some of the sub-cortical grey matter voxels were misclassified as white. This became apparent when SPM map showing regions of increased white matter volume was overlaid on the structural image representing the averaged brain of the patient group. A presumed sub-cortical region of increased white matter had fallen onto the

posterior putamen. This registration error was rectified with optimised VBM. Therefore, only the results of the optimised VBM were reported and are discussed next.

The optimised protocol revealed global and regional structural volume alterations in patients. Global alterations encompassed reductions in the volume of both grey (by 9%) and white matter (by 7%), and, consequently, that of the whole brain (by 9.5%). The present finding adds to the weight of evidence for reduced white matter availability in schizophrenia patients as compared to healthy individuals, since previous studies did not find the white matter reduction as consistently as that of the grey matter (Lawrie and Abukmeil, 1998).

Regional alterations observed in the present sample were confined to the left hemisphere (although statistical parametric map displayed a right hemisphere reduction of IFC volume, it was not significant according to the criteria specified in the Method section). Regional alterations included significant grey matter volume reductions of IFG (BA 47/45), LG (BA 17), and STG (BA 38; significant with SVC), and significant (with SVC) grey matter volume of the putamen. Additionally, few reductions were significant at less than 1% level uncorrected, but did not survive multiple comparisons correction, including white matter volume of the posterior and occipital lobes, as well as increased grey matter volume of the precuneus (BA7).

Most of these findings are in agreement with other recent VBM studies. The left IFG and OL white matter volume reductions are in line with the findings of Ananth and colleagues (2002), who were the first to employ optimised volumetric VBM protocol, although the region of maximal effect for IFG in their study was more superior (BA 46) [x y z = -45 15 36], bordering the middle frontal gyrus (BA 9). The reduction of the IFG grey matter concentration has also been observed with VBM (Wright et al., 1999; Wilke et al., 2001; Suzuki et al., 2002). One ROI study (Buchanan et al., 1998) reported reduced volume of both left and right IFG.

The patients had reduced grey matter volume of the LG (BA 17). Selemon and colleagues (1995) reported increased neuronal density (a marker of neuronal atrophy) in BA 17 in post-mortem brains of schizophrenia patients. Reduction of the grey and white matter in the primary visual cortex was recently reported to associate with poor-outcome schizophrenia patients (Mitelman et al., 2003). Four earlier ROI studies measuring the occipital lobe as a whole have reported a reduction of this region (Andreasen et al., 1994; Bilder et al., 1994, 1999;

Zipursky et al., 1992). One VBM study (Job et al., 2002) observed grey matter concentration reduction in the cuneus, which is immediately adjacent to the area of reduced volume in the present cohort. The findings of the present study suggest that greater LG volume reduction might be associated with more severe form of the illness, as it positively correlated with the number of previous psychotic episodes. This, in fact, replicates the finding by Mitelman et al. (2003) of poor clinical outcome in patients having a greater reduction of the primary visual cortex.

STG grey matter volume reduction has 100% replicability using ROI approach (Shenton et al., 2001), with the reduction of the anterior part found more consistently than that of the posterior part (Rajarethinam et al., 2000). VBM concentration studies have found left STG grey matter volume reductions specific to the anterior part (Wright et al., 1999; Wilke et al., 2001; Kubicki et al., 2002). The anterior STG grey matter reduction might also be specific to schizophrenia, since it was one of the areas to differentiate patients with schizophrenia and bipolar depression (Pearlson, 1997). Recently, Kasai and colleagues (2003) reported progressive changes in both anterior and posterior STG grey matter volume in first-episode patients 1.5 years following the initial hospitalisation. The present investigation, however, did not observe an association between STG grey matter volume and illness duration. What was observed is smaller STG volume in patients with family history of schizophrenia than in patients with no family history. It is possible that in patients with genetic loading STG volume reduction might represent a neurodevelopmental anomaly with possible further degeneration following the illness onset.

Putamen enlargement has been observed in schizophrenia with both ROI (Gur et al., 1998; Hokama et al., 1995) and VBM (Wilke et al., 2001; Saldago-Pineda et al., 2003) methods. The putamen increase might be associated with neuroleptic exposure (e.g. Gur et al., 1998); however, the present study did not observe such an association. It must be noted that the use of chlorpromazine equivalents may result in a distorted estimate of the current neuroleptic exposure, and thus the possibility of the putamen increase being due to the neuroleptic use cannot be completely discounted. Buchsbaum and colleagues (2003) have recently reported increased putamen size in good, but not in poor, outcome schizophrenia patients, which was not related to either current or accumulative neuroleptic exposure, and suggested that larger putamen might simply represent a physiological correlate of neuroleptic responsiveness. The observed association of larger putamen with less

severe positive and general psychopathology symptoms in the present cohort provides an indirect support for this notion.

The increase in the grey matter concentration of the precuneus (bilaterally) was previously observed in female, but not male, patients with VBM (Suzuki et al., 2002). Another VBM study (Wilke et al., 2001) reported the bilateral reduction of CSF concentration above the precuneus. The present study provides further evidence for the grey matter increase in the precuneus, now with the volumetric approach and regardless of gender, and suggests that larger left precuneus is associated with more recurrent form of psychosis, by positively correlating with the number of previous psychotic episodes and hospitalisations. However, two VBM studies that used in-house processing techniques rather than protocols implemented in SPM, reported reduction in grey matter concentration of the precuneus on the left (Shapleske et al., 2002) as well as bilaterally (Hulshoff Pol et al., 2001). The regions within the precuneus implicated in these studies were more ventro-medial than the ones observed in this study (which was bodering parieto-occiptial sulcus) and other VBM studies using SPM.

To the best of author's knowledge, the present study is the first to observe white matter volume reduction in the white matter region that includes the fibres of the posterior extent of SFL in schizophrenia. SFL is a long association tract and is the most important one for language function, as it establishes communication between area triangularis of the inferior frontal lobe, BA 22 in the temporal lobe, and the angular and supramarginal gyri in the parietal lobe. A severing of a part of this tract known as the *arcuate fasciculus* in the dominant hemisphere disconnects the anterior speech area (Broca's area) from the posterior language area (Wernicke's area), resulting in conduction aphasia (inability to repeat what is heard). Reduced volume of the posterior SFL, near the inferior parietal lobule, might have implication for language function.

The present study did not observe predicted reductions of hippocampal complex. It could be argued that the VBM might not be sensitive enough to identify these abnormalities, due to the difficulty in differentiating grey and white matter in these areas (Velakoulis et al., 1999; Ashburner and Friston, 2000). In addition, 12mm smoothing kernel creates local weighted volumes that are larger than the size of the hippocampus, thus potentially hampering the detection of possible abnormalities in hippocampal complex. Therefore, the lack of findings in this area might be due to the limitations of the VBM method and the choice of the smoothing kernel size. However, previous VBM studies have been able to detect

abnormalities in the medial temporal lobe structures, including reduction of the right amygdala (with 12mm smoothing kernel; Wright et al., 1999; Job et al., 2002), parahippocampal gyrus (with 12mm, Job et al., 2002), left hippocampus (with 6mm, Kubicki et al., 2002), and bilateral hippocampus (with 12mm, Suzuki et al., 2002). To ascertain that the lack of the hippocampal finding is not due to the selection of 12 mm kernel, the data were re-analysed with 10mm and 6mm smoothing kernels; however, no differences were observed in the hippocampal complex even at the most liberal threshold of $p<.05$ uncorrected.

The present study did not observe any alterations of some regions that have been relatively consistently replicated in VBM studies. One such region is insula, which was neglected by ROI studies, and has emerged due to the VBM approach as the area implicated in schizophrenia neuropathology. Three VBM studies (Wright et al., 1999; Wilke et al., 2001; Kubicki et al., 2002) have reported grey matter concentration reduction of the insula. However, Ananth et al. (2002) who applied volumetric VBM did not observe insula alteration. Therefore, the reduction of insula might be limited to grey matter concentration, i.e. to the amount of grey matter relative to other brain tissues in this region. Another region that has been replicated by three VBM concentration studies (Job et al., 2002, Kubicki et al., 2002; Suzuki et al., 2002), but not VBM volume study (Ananth et al., 2002) is anterior cingulate (AC). The present study did not observe AC volume reduction, suggesting that AC reduction might also be limited to the concentration. Third region showing relative consistency in being implicated is orbito-frontal cortex (OFC), which was observed with both concentration (Wilke et al., 2001) and volume (Ananth et al., 2002) measurements. Overall, the pattern of structural alterations identified by different VBM studies differs and sometimes substantially. Factors such as differences in the patient populations and sample compositions (e.g. gender of the patients, age, etc), variations in the pre-processing steps, the choice of covariates (e.g. total grey matter, whole brain volume, intra-cranial volume) amongst possible others are all contributing factors to variations in findings. The pattern of the structural alterations of the present study is generally consistent with the previous literature.

Contrary to the prediction and to the findings of the previous studies (Tien et al., 1996; Woodruff et al., 1997b; Bullmore et al., 1998), the volumes of the frontal and temporal cortices were found to be associated in schizophrenia patients to a similar extent as in normal controls. The present study investigated the relationship between much more specific areas and specific tissue compositions, than studies that observed fronto-temporal dissociation in schizophrenia patients

(Tein et al., 1996; Woodruff et al., 1997b; Bullmore et al., 1997). The only other study (Wible et al., 1995) to look at separate tissue compositions have observed relationship between the volume of left PFC grey matter and reduced volume of STG in schizophrenia patients; however, the difference between patients and controls was not assessed formally and, therefore, it is not clear whether the finding was specific to schizophrenia. Interestingly, Woodruff and colleagues (1997b) observed no association between the volume of ventrolateral PFC, which included IFG, and the volume of STG either in patients or controls. It is possible that the association might be specific to grey matter volume, as found in the present study. Alternatively, the dissociation might be specific to male patients (Woodruff et al., 1997b; Bullmore et al. 1997). However, in the present study the effects of age and gender were controlled for at all stages of the analysis, and thus the association between these two regions existed regardless of gender. Finally, in the previous studies the patients did not differ from the controls on the volume of the ROI that were found to be associated in controls but dissociated in patients. The present study was specific to investigating the inter-relationships between regions which volumes were altered relative to normal controls. Basolateral frontal cortex is connected with anterior temporal cortex through a thick bundle of relatively short white matter fibers called *fascisulus uncinatus*. The IFG and the anterior STG show functional correlation in the tasks requiring semantic processing and memory (e.g. Binder et al., 1997; Rao et al., 1997; Mummery et al., 1999). The co-reduction in the volumes of these regions (independent of total grey matter volume) suggests structurally compromised neural network involved in language and meaning related processing in at least some patients (the correlations between the volumes of these regions were modest). Shergill et al. (2000) reported functional disconnection between IFG and STG in patients prone to auditory hallucinations, presumably resulting in impaired verbal self-monitoring.

The IFG volume reduction in patients was also positively associated with that of LG. This association was much weaker in controls. Curiously, although the grey and white matter volume reduction of the occipital lobe were correlated, IFG grey matter volume reduction was associated with only grey matter volume of LG. Other positive inter-relationships between altered tissue volumes in patients were observed between spatially related regions, including two regions of STG grey matter volume, and grey and white matter volumes of the occipital lobe. These associations were also strong in normal controls. Further, larger putamen volume was associated with smaller white matter volume of SFL, with this volume inter-relationships being specific to schizophrenia (i.e. significantly differentiating the

groups). On the other hand, patients lacked 'normal' inter-relationships between larger precuneus and smaller SFL, as well as larger STG grey matter and larger OL white matter volumes. The findings pertaining to these volume inter-relationships are open to interpretation. Not much is known about the cortical volume inter-development and inter-relationships in normal or affected populations. A relative lack of strong and consistent inter-relationships between structural volume alterations in the patients, except for the spatially related areas such as LG grey matter and OL white matter, and two voxels of the STG, suggests that there is a considerable variability in the pattern of structural alterations amongst the patients, with individual patients presenting with some but not all of the observed alterations. For example, based on the observed correlations, increased precuneus cannot be said to represent a compensatory feature, since its volume did not significantly correlate with the reduction in other regions.

Some structural alterations were associated with the severity of psychopathology. First, the severity of positive symptoms was associated with global grey matter reduction, but not with any regional reduction, suggesting that positive symptomatology might be a manifestation of the widespread alteration in grey matter tissue availability. Alternatively, the use of positive symptom scale rather than individual symptoms for correlations potentially may mask any specific region/symptoms associations. For example, auditory hallucinations were found to associate with the anterior STG reductions (Barta et al., 1990), whereas delusions with the posterior STG reduction (Menon et al., 1995). Positive syndrome score derived from PANSS contains other items apart from hallucinations, which might have masked the relationship between STG volume and hallucinatory experiences. However, when hallucination ratings were correlated with the anterior STG volume (not reported in the results section), the correlations observed, although in the right direction, were not significant (r = -.166 and -.137; p = .282 and p = .376). Second, increase in the putamen volume was associated with *less* severe positive symptoms and general psychopathology ratings. As has been discussed earlier, a possible interpretation of this association is that larger putamen allows better neuroleptic responsiveness. Third, greater reduction of SFL white matter was associated with *lower* ratings on general psychopathology. This is a counter-intuitive association, which is open to interpretation, as this area in relation to schizophrenia psychopathology is unknown. Finally, negative symptoms did not associate with any of the structural alterations. In previous research, the severity of negative symptoms was found to associate with the volumes of PFC grey matter (Chua et

al., 1997; Molina et al., 2003a), PFC white matter (Wible et al., 2001) and DLPFC CSF (Flaum et al., 1995; Molina et al., 2003b). In addition, Schroder et al. (1995) reported an association between negative symptoms and frontal interhemispheric fissure widening in chronic patients. Other studies, however, have failed to relate prefrontal grey matter volume reduction and negative symptoms (Wolkin et al., 1992; Gur et al., 2000; Molina et al., 2003b). It appears from these findings that PFC CSF increase is found to be associated with negative syndrome more consistently than PFC grey matter reduction, which might be indicative of degenerative rather than developmental processes as the basis for negative symptomatology. Alternatively, different methodologies and patients' characteristics might explain the inconsistency in findings. For example, Chua et al. (1997) observed association between psychomotor poverty, as defined by Liddle (1987), and ventro-medial PFC grey matter volume, whereas other studies have correlated PANSS- or SANS- derived negative syndrome scores with the variety of general and regional PFC measurements.

What might be the reasons for a misregistration of the images with the standard protocol? The standard SPM99 whole brain template for T1-weighted images, which was used to normalised brains during the standard pre-processing, is an average of 152 MRI scans of young healthy brains, as has been described in the introduction. This template might not be optimal for normalisation of the brains from the populations that have substantial deviations from the normal brain morphology, e.g. enlarged ventricles, as presented in the case of schizophrenia patients. Because of the high contrast between brain tissue and CSF, the spatial normalisation will attempt decreasing the sizes of extra large ventricles by shrinking all the tissue surrounding this region, which has the effect of 'pulling in' grey matter towards the centre of the brain (John Ashburner, personal communication). Therefore, the normalisation of patients' brains to the MNI template might have created a displacement of grey matter voxels adjacent to and surrounding the region of the lateral ventricles. Spatially normalising based only on the grey matter in the optimised procedure avoids this problem. Furthermore, the use of customised probability maps of grey matter constructed from the brains of both patients and controls during the optimised pre-processing should further decrease the bias in the processing of patients' brains. It is not possible to evaluate the relative contribution of these factors to the improved processing with the optimised protocol in the present study. The systematic investigation of the absolute and relative importance of grey matter normalisation and the use of customised templates for the pre-processing of brains of

schizophrenia patients is needed to understand the contribution of different processing components to segmentation accuracy.

In fact, this issue is of great empirical importance. Wilke and colleagues (2003) have recently reported the results of the systematic investigation of the effect of different features constituting standard and optimised VBM protocols amongst other variables that they have manipulated on the detection of grey matter malformations in epilepsy. Their results revealed that the simplest protocol with affine transformation only during spatial normalisation was the most sensitive in identifying cortical malformations. The optimised protocol was inferior, 'missing' a few regions. The results of this investigation are not directly applicable to the case of schizophrenia, since there are no 'gross' cortical malformations associated with this condition. Nevertheless, the study raises an important question as to the sensitivity of different methods of processing in the case of schizophrenia. Thus, the future work should systematically manipulate different variables constituting the VBM pre-processing steps. It might be the case, for example, that the use of the customised whole brain template with standard protocol is equivalent, if not superior, to the optimised procedure described by Good and applied in this study in the detection of structural alterations of a kind present in schizophrenia patients.

The observed misregistration with standard protocol in the present study also raises a question as to the validity of the findings by previous VBM studies of schizophrenia patients that have used standard VBM protocol with MNI template for spatial normalisation (e.g. Suzuki et al., 2002; Kubicki et al., 2002) or customised templates containing information only from normal subjects (e.g. Job et al., 2002; Ananth et al., 2002).

To conclude, the present study identified both global and regional volume alterations of grey and white tissue in schizophrenia patients. The alterations span all cortical lobes of the left hemisphere, and extend sub-cortically into putamen. These alterations were present in patients as a group regardless of gender or age, and were unrelated to medication exposure. They were not related to the duration of the illness, suggesting neurodevelopmental origin. Some alterations, including the reduced white matter of the primary visual cortex and SFL and increased grey matter of the precuneus, might be related to the course of the illness. The study has highlighted the need for using the pre-processing protocols that treat patients' brains in the unbiased way by normalising to grey matter as opposed to the whole brain and/or by using the

customised templates containing information from both patients and controls to avoid spatial distortions of patients' brains that might arise due to enlarged ventricles. Finally, it is important to view regional differences in schizophrenia patients detected in the present study as representing foci of maximal change, rather than regions that are exclusively or selectively affected, since the VBM technique may not be able to detect very small grey matter reductions, grey matter reductions in areas of hight variability in grey matter volume, or grey matter reductions with an inconsistent location.

CHAPTER 6. COGNITIVE DEFICITS IN SCHIZOPHRENIA

6.1. Introduction

Individuals with schizophrenia display well documented cognitive deficits (reviews, Elvevag and Goldberg, 2000; Kuperberg and Heckers, 2000; Sharma and Antonova, 2003), which i) precipitate the psychotic symptoms (Weickert and Goldberg, 2000); ii) are relatively stable over time with progressive deterioration after the age of 65 in some patients (Friedman et al., 2001); iii) persist upon the remission of psychotic symptoms (Heaton et al., 2001); and iv) are related to, but separate from, negative symptoms (Harvey et al., 1996; Hughes et al., 2003). Most importantly, cognitive deficits are better predictors of functional outcome than the psychotic symptoms (Green, 1996), which have made them the primary target of therapeutic intervention over the past decade (Sharma, 2002).

Delays in reaching developmental milestones, neuromotor and visuo-motor anomalies, and cognitive deficits are apparent throughout the premorbid history of schizophrenia patients (Jones and Tarrant, 2000). It is well established that schizophrenia is often associatied with impairment in general intellectual functioning (review, Aylward, Walker, & Bettes, 1984). It is not clear if impaired IQ represents a decline due to a disease process or a premorbid deficit. Retrospective and high-risk studies reported that individuals who develop schizophrenia have lower premorbid IQ than siblings and peers matched for parental socio-economic status (review, Aylward et al., 1984). The 19-year prospective study (Kremen et al., 1998) has found that IQ decline between the ages of 4 (as measured by the Standford-Binet IQ test; Terman and Merrill, 1960) and 7 years (as measured by the abbreviated version of the Wechsler Intelligence Scale for Children (WISC); Wechsler, 1949) was predictive of adult psychotic symptoms in a community birth cohort. Therefore, it is likely that impaired IQ in schizophrenia might be a result of the process starting early in the development and presenting a risk factor for psychosis.

In addition to lower general intelligence, a wide spectrum of cognitive domains has been consistently shown to be impaired in first episode and chronic schizophrenia patients between one and three standard deviations below the mean of age-matched controls, including verbal and visuo-spatial working memory, learning and memory, executive function, attention, verbal fluency, speed of information processing and fine motor function (e.g. Nuechterlein and Dawson, 1984; Waddington et al., 1990; Green et al., 1992; Hoff et al., 1992; Braff et al., 1993; Saykin et al., 1994; Bilder et al., 1995; Hutton et al., 1998; Riley et al., 2000; Bilder et al., 2000). These deficits cannot be explained solely by the chronic administration of neuroleptic medication, since these deficits are also observed in neuroleptic naïve first episode patients to a similar extent (Saykin et al., 1994). However, neuroleptic medication as well as adjunct cholinergic treatment has adverse effects on some cognitive functions in schizophrenia (Frith, 1984; Medalia et al., 1988; Spohn and Strauss, 1989; Cassens et al., 1990; Kumari et al., 2003b; Ettinger et al., 2003). Anticholinergic procyclidine is also known to impair cognitive function in healthy humans (e.g. Kumari et al., 2001; Zachariah et al., 2002).

Meta-analysis (Heinrichs and Zakzanis, 1998) of 204 studies of schizophrenia patients relative to healthy individuals revealed moderate to large effect sizes (d >.60) for 22 neuropsychological test variables, tapping the domains of general intelligence, verbal and nonverbal memory, motor performance, visual and auditory attention, spatial ability, executive function, language, and inter-hemispheric transfer. Although this pattern of cognitive impairment points to a generalised deficit, there is evidence to suggest that verbal learning and memory, working memory (its executive component) and attention might be specifically affected in the background of general cognitive impairment (review, Gur, Moelter, and Ragland, 2000).

The primary aim of this study was to characterise the pattern of cognitive deficits in the present cohort for the subsequent investigations: Study 3 (*Chapter 7*): The relationships between structural alterations and cognitive deficits; and Study 4 (*Chapter 8*): Structural Alterations as Predictors of Treatment Response following 6-week Treatment with Atypical Antipsychotics. The nature of this study was replicatory. To suit the present aims, the cognitive domains and individual neuropsychological tests tapping the domains of interest were selected based on the following criteria (as validated by the previous research):

1. To reliably differentiate schizophrenia patients from healthy individuals and to be commonly used in schizophrenia research to ensure generalisability of findings from the present study to those of previous research.
2. To be unaffected or worsened by the conventional antipsychotics.
3. To be sensitive to improvement with atypical antipsychotics.
4. To have relevance to functional outcome in schizophrenia.
5. To have high test-retest reliability.
6. To have alternative form(s) for repeated administration to minimize practice-effect.

The fulfilment of the first and the second, the first and the third, or the first and the fourth criteria was held as obligatory for all domains/tests selected for the investigation. The fulfilment of any additional criterion was held as desirable, because not all tests that have proven useful in the study of treatment response and functional outcome in schizophrenia have these properties.

The cognitive domains selected based on these criteria were immediate and long-term verbal memory and learning, verbal working memory, verbal fluency, immediate visuo-spatial memory, executive function, memory for social stories, selective and sustained attention, speed of information processing, and fine motor function. The description of individual neuropsychological tests selected to measure these domains and the fulfilment of the above criteria by each test is provided in the Method section.

Based on the observations of previous research, it was predicted that schizophrenia patients would perform significantly worse on all cognitive domains, with specific impairments on the tests of verbal learning and memory, working memory and attention. Since high doses of conventional antipsychotic and anticholinergic treatment have an adverse effect on learning and memory, the severity of the impairment on this function was predicted to be associated with the current medication dose of antipsychotic and anticholinergic treatment.

6.2. Methods

6.2.1. Participants

The information on patient and control groups is presented in Chapter 5.

6.2.2. Neuropsychological Battery

The tests comprising the neuropsychological battery described below are grouped *a priori* into cognitive domains for the presentation only based on the cognitive processes that these tests are considered to measure (Lezak 1995, Spreen and Strauss, 1998). It must be noted, however, that each neuropsychological test is likely to require a complex composite of cognitive operations for performance, involving specialised processors, as well as non-specific strategic control processes. Therefore, when the test is said to measure a specific domain, it is presumed that the test places the highest demand on this domain for the optimal performance; but might involve one or more of other domains.

6.2.2.1. General Intellectual Functioning: Premorbid and Current IQ

National Adult Reading Test, restandardised version (NART-R; Nelson and Willison, 1991), was used to assess premorbid intellectual ability. Premorbid IQ constitutes the level of intellectual ability prior to the onset of a disorder, psychiatric or neurological, or the occurrence of brain lesion. The NART was chosen since it is the most common test used in schizophrenia research to estimate premorbid intelligence. It requires reading 50 irregularly spelled words (e.g. debt, catacomb, naïve) in order of increasing difficulty. The rationale for the irregularly spelled words is to ensure that the subject's reading is based on word recognition rather than phonemic decoding. The NART is assumed to measure premorbid intelligence since the word-reading ability is highly (0.75) correlated with general intelligence in healthy individuals (Nelson and McKenna, 1975) and is remarkably preserved in dementing patients with substantial cognitive deterioration (Nelson and O'Connell, 1978). The number of errors is used to estimate the premorbid WAIS-R Full Scale IQ.

Some studies of neuropsychological function in schizophrenia have matched patients and controls on premorbid IQ in order to estimate the extent of cognitive dysfunction independent of premorbid general intelligence. However, most studies did not match patients and controls on premorbid IQ. Such matching was

not attempted for the purposes of the present investigation. Since IQ decrement in schizophrenia population might be associated with the disease aetiology and be a manifestation of an underlying neurodevelopmental pathology, matching groups on IQ would inadvertently lead to 'matching fallacy' (Meehl, 1970) and create a sampling bias towards more intelligent non-representative schizophrenia sample. As described in Chapter 5, the groups were matched on parental socio-economic status instead, since parental social class is the best predictor of IQ in normal controls (Keefe, 1995).

The ***Vocabulary*** sub-test of the ***Wechsler Adult Intelligence Scale***, third version (WAIS-III, Wechsler, 1997) was used to assess subjects' current full-scale IQ. The Vocabulary sub-test has been traditionally held to represent the single best indicator of the current intellectual ability (Yates, 1954). Russell and colleagues (2000) in a retrospective study have found that the Vocabulary sub-test of WAIS-revised was the strongest index of premorbid as well as current full scale IQ. Based on these indicators, only the Vocabulary subtest was administered rather than all WAIS-III subtests to minimize the time required for the completion of neuropsychological assessment and hence to ensure optimal performance from patients in a single session.

The test requires giving brief and precise definitions to both concrete and abstract words (nouns, verbs, and adjectives). The words are presented in the order of increasing difficulty. The test is discontinued after 6 consecutive failures to provide a definition. Age scaled scores were used to calculate the pro-rated full scale IQ. By treating the scores as the average of the 6 sub-tests constituting the verbal IQ of WAIS-III, verbal IQ was estimated first, from which the full IQ was derived using Tables A.3. and A.5. of the WAIS-III manual respectively.

6.2.2.2. Executive Function

Wisconsin Card Sorting Test (computerised version) (Heaton, 1993)

Test description:

The WCST assesses the ability to form abstract concepts and flexibility of thinking. A participant is presented with a card at the bottom of a computer screen and is asked to match the card to one of the four cards at the top of the screen. The test requires an individual to work out a sorting rule for the cards

that can be categorised by three dimensions: shape, colour and number of items on the card. After each match, a participant is given feedback whether the decision was right or wrong. After 10 consecutive correct matches the sorting category shifts to a different dimension. This requires a participant to be flexible in his/her responses by abandoning a previously successful sorting rule and learning a new one. The first sorting category is colour, which then changes to shape and then to number and this sequence is repeated once. 128 cards are administered in total in this version of the test.

The WCST requires a number of cognitive processes for a successful performance, including the ability to abstract and categorise stimuli, to come up with a strategy, to shift mental sets (set-shifting) in response to the changed rules, and to inhibit an established (pre-potent) response. To characterise the WCST in terms of these processes, the WCST yields several scores, such as categories completed, number of errors, perseverative responses/errors, conceptual level responses and failures to maintain set. Categories completed and perseveration (responses or errors) are most commonly used in schizophrenia research, with perseverative responses being shown to be the most sensitive and specific to the nature of executive dysfunction observed in schizophrenia patients (Koren et al., 1998).

Dependent variable:

The total number of perseverative responses was selected as the dependent variable on the WCST. Perseverative response occurs when the previously successful strategy is continually used in the face of a changed rule and hence is the index of the ability to inhibit a pre-potent yet redundant response and to shift strategy in response to environmental feedback. Higher score represents poorer performance (i.e. greater perseveration).

Fulfilment of the selection criteria:

This test was selected as it is the single most widely used measure of executive function in schizophrenia research, as well as in the general neuropsychological practice and research (Butler et al., 1991). The WCST performance consistently differentiates patients from controls. Since the initial study by Fey (1951), over 150 studies were published implicating impaired WCST performance in schizophrenia (Palmer and Heaton, 2000). The WCST performance has been

linked to functional outcome, with perseveration index found to be predictive of social adjustment (Jaeger and Douglas, 1992), social competence and occupational functioning (Velligan et al., 2000).

The WCST does not have high test-retest reliability in normal subjects, since it is susceptible to practice effects. It has been argued that once administered, the WCST no longer measures problem-solving ability (Lezak, 1995). This of course is inevitable with any true measure of executive function, since the executive function is by definition employed to tackle novel tasks and situations. Once a situation has been encountered and a strategy developed, given the subject has an intact memory, the retest performance will be guided by one's memory of the task. Schizophrenia patients treated with conventional neuroleptics do not show normal test-retest gains in task performance (e.g. Goldberg et al., 1987), presumably due to the effects of sub-cortical dopaminergic blockade on episodic memory inhibiting the memory-dependent improvement (Robbins et al., 1990). However, patients with less severe general cognitive impairment show improvement with repeated exposure (Green et al., 1990; Bellack et al. 1996). The WCST performance has been found to improve with novel antipsychotics such as clozapine, risperidone and olanzapine, although negative findings have also been reported (review, Meltzer and McGurk, 1999). Therefore, any potential improvement on the WCST with repeated administration after the switch to atypical antipsychotics (Study 4) should be interpreted with caution, since it might occur due to the improvement of executive function itself or episodic memory.

Trail Making Test (Reitan and Wolfsonk, 1993)

Test description:

This test has two parts, A and B. Part A requires a subject to join the circles containing numbers from 1 to 25, which are scattered on the A4 sheet, in ascending order as quickly and as accurately as possible. Optimal performance on part A primarily depends on efficiency of visual scanning and psychomotor speed (Spreen and Strauss, 1998). Part B demands the employment of executive function, particularly mental flexibility, since it requires the subject to join the numbers in ascending order from 1 to 13 alternating with letters in alphabetic order from A to L that are randomly scattered on an A4 sheet. Apart from placing demands on visual scanning and psychomotor speed, part B also requires greater attention and working memory than Part A.

Normally parts A and B are scored separately, with the score represented by the time to complete in seconds. A difference score, subtracting the time on Part A from the time on Part B, can be used to factor out the effects of psychomotor speed (Buchanan et al., 1994). Although the difference score has not been as widely used as the scores for Part B alone, it is recommended (Palmer and Heaton, 2000), since it allows isolating the effects of mental flexibility deficits from psychomotor slowing, which can be a side effect of conventional antipsychotics.

Dependent Variable:

Following the recommendation of Palmer and Heaton (2000), the difference score Part B *minus* Part A (Part B – Part A) was used as an index of mental flexibility.

Fulfilment of the selection criteria:

Trail Making Test is extensively used in schizophrenia research and is consistent in differentiating schizophrenia patients from normal controls (e.g. Braff et al., 1991; Franke et al., 1993; Bilder et al., 1991; 1995; 2000; Saykin et al., 1994; Riley et al., 2000). In the meta-analysis of 204 studies (Heinrichs and Zakzanis, 1998), the test was found to separate more than half of the patients and control distributions. Trail Making performance is sensitive to treatment with atypical antipsychotics risperidone (Meltzer and McGurk, 1999) and quetiapine (Fleming et al., 1997). Olanzapine was not found to have a positive effect on Trail Making performance in the study of neuroleptic resistant schizophrenia patients (Meltzer and McGurk, 1999), however treatment resistant sub-group is not representative of the schizophrenia population at large. Trail Making was not found to be predictive of community outcome in schizophrenia patients (Goldman et al., 1993; Buchanan et al., 1994). However, Trail Making performance might be more relevant to occupational outcome and skill acquisition, but these outcome variables have not been as yet assessed in relation to the Trail Making deficit.

Test-retest reliability is .98 for Part A and .67 for Part B in normal subjects, with significant practice effects only on Part A over three administrations in 6 month intervals. Durvasula et al. (1987) reported significant practice effects for both parts at 6-month testing intervals, which flattened after 5 administrations.

Therefore, any improvement on TMT in Study 4 will have to be interpreted with caution taking the practice effects into account.

6.2.2.3. Sustained and Selective Attention

Continuous Performance Test, Identical Pairs Version (CPT-IP) (Cornblatt et al., 1988)

Test description:

This test was designed to assess the ability to sustain attention. Subject's task is to identify the pairs of identical numbers within a continuously presented string of four digit numbers, which are flashed up on a computer screen at a rate of one per second with an 'on' screen time of 50 ms. Subjects are asked to hold the left mouse button of a computer continuously throughout the test lifting the finger up quickly and putting it back again when the subject spots a number which is identical to the one before. There are also a number of catch trials on which the stimulus presented is similar to the preceding one, but not identical to it. There are 450 numbers presented overall with 90 response targets and 90 catch trials.

Individual performance on the CPT-IP task is based on hits (responses to target trials) and false alarms (responses to catch trials) yielding two signal detection indices:

d'prime – representing signal to noise ratio and measuring sensitivity of the subject to discriminate targets from catch trials;

beta – criterion of the subject to respond to target or catch trials, i.e. under or over-responding.

Depended variable:

d' prime was used as the dependent variable, since it is the measure of sustained attention.

Fulfilment of the criteria:

CPT – IP is the single most often used measure of sustained attention (vigilance) in schizophrenia research (Neuchterlein and Dawson, 1984), and is very sensitive to the attentional impairment in schizophrenia patients (e.g. Strauss et al., 1993)

and in individuals at high risk (e.g. Cornblatt and Keilp, 1994). CPT performance is impaired by acute (1-3 days) administration of conventional antipsychotics (Latz and Kornetsky, 1965), but shows some improvement with chronic administration (review, Medalia et al., 1988). However, improvement is greater with novel antipsychotics, including risperidone (Stip and Lussier, 1996; Rossi et al., 1997; Kern et al., 1998), olanzapine (review, Meltzer and McGurk, 1999) and quetiapine (review, Velligan et al., 2002). Attentional dysfunction as assessed by CPT combined with other measures of attention is predictive of different aspects of functional outcome, including social problem solving (Bowen et al., 1994; Penn et al., 1995) and skill acquisition (Bowen et al., 1994; Corrigan et al., 1994; Kern et al., 1992).

CPT – IP has high test-retest reliability (ranging from .56 to .73 for d'prime, Cornblatt et al., 1988), making it ideal for the studies with repeated assessments. However, practice effect is also robust and has to be controlled for, although it is minimal for d'prime index (Cornblatt et al. 1988).

Stroop Test (Golden, 1978)

Test description:

This test was designed to test the inhibition of pre-potent response that requires selective attention to the stimuli. A subject is presented with a list of 100 colour words and is given 45 sec to name as quickly as possible colours in which these colour words are written. The challenge lies in the fact that the words are written in colour ink that is incongruent with the colour for which this word stands for. For example, response to the word RED typed in BLUE colour should be BLUE. The effect of this test is understood to be due the requirement to actively inhibit a more automatic (and hence quicker processed) tendency to read words in favour of the less automatic (or slower processed) colour naming (Dyer, 1973). Two control tasks, reading of the colour words typed in congruent colour over 45 sec and naming the colours over 45 sec, are administered in conjunction with the main task to control for individual differences in the speed of reading and colour naming respectively. The number of words read and colours named at each stage of the test is recorded.

Dependent variable:

The depended variable is the interference score, which is the difference between a predicted colour word (CW) score and the raw CW score. Predicted CW score is calculated from the following formula: C x W/C + W, where C is the number of colours named in 45 seconds and W is the number of words in congruent colours read in 45 seconds.

Fulfilment of the selection criteria:

Stroop task, or as it is also called Golden Stroop, is widely used within schizophrenia research as a measure of selective attention or inhibition (review, Pearlstein et al., 1998), and it can be subsumed under a more general domain of executive function (Lezak, 1995; Spreen and Strauss; 1998). The interference score produces a large effect size (d = 1.22) in schizophrenia studies as revealed by meta-analysis (Heinrichs and Zakzanis, 1998). Stroop performance is unaffected by chronic administration of conventional antipsychotics (e.g. Killian et al., 1984), but shows improvement with atypical antipsychotics, such clozapine (Buchanan et al., 1994) and quetiapine (Velligan et al., 2002). It has been also found to associate at trend level with community outcome (Buchanan et al., 1994).

All three parts of the Stroop test show high test-retest reliability with the coefficients of .90 for the word reading, .83 for the colour naming, and .91 for the colour-word part in normal subjects (Spreen and Strauss, 1998). However, significant practice effect is also observed, and therefore should be controlled for.

6.2.2.4. Verbal working memory

Letter-Number Test (Gold et al., 1997)

Test description:

Letter-number test (LNT) assesses subject's ability to retain and manipulate mentally common verbal stimuli in working memory, and thus employs central executive component of working memory. A subject is presented with verbal strings comprised of randomly ordered numbers and letters. The task is to listen to the string and to repeat it back in a certain order, putting the numbers first in ascending order followed by the letters in the alphabetic order. Increasingly

longer strings are presented starting from two stimuli (one letter, one number, e.g. D6) and finishing with the string of seven stimuli (three numbers and four letters, e.g. C7G4Q1S, or four numbers and three letters, e.g. 3T4P7M9). Each level of complexity is comprised of 4 different strings, bringing the total number of strings to 24. The test is discontinued after a subject fails all four trials at a given string length.

Dependent variable:

The dependent variable is the total number of strings reproduced correctly. The scores range between 0 and 24, with higher score indicating better performance.

Fulfilment of the selection criteria:

LNT captures the essence of executive working memory component so well, that it has been incorporated into the most recent versions of both the Wechsler Adult Intelligence Scale (WAIS-III) and the Wechsler Memory Scale (WMS-3). Both chronic and first episode schizophrenia patients show large deficit on this task (e.g. Park and Holzman, 1993; Gold et al., 1997; Riley et al., 2000; Pukrop et al., 2003). No published study was found purporting to the effects of conventional antipsychotics on LNT, perhaps because LNT has been relatively recently adopted for the study of auditory working memory in schizophrenia. Other tests of auditory working memory such as Digit Span forward and backward do not seem to be affected by either acute or chronic administration of conventional antipsychotics (e.g. Abrams, 1958; Castner et al., 1958; Pearl, 1962; Small et al., 1972;). Auditory working memory as measured by LNS and digit span tasks might be improved with risperidone, but not olanzapine (review, Meltzer and McGurk, 1999) or quetiapine (Velligan et al., 2002).

Letter-Number Sequencing task, which is a derivative of the LNT task adopted for WAIS-III and WMS-III, has high test-retest reliability (0.71) and shows minimal practice effects at 2 to 12 weeks retest interval. Therefore, LNT task was considered to have satisfactory psychometric properties for the repeated administration.

6.2.2.5. Visuo-spatial immediate memory

Benton Visual Retention Test (Benton, 1972)

Test description:

Benton Visual Retention Test (BVRT) assesses visual memory, visual perception, and visuoconstructive abilities (Spreen and Strauss, 1998). A subject is presented with 10 designs of abstract shapes in the order of increasing complexity. First two designs contain one large central geometric figure, while the other eight contain two larger central and one small peripheral figure. Each picture is presented for ten seconds, after which it is withdrawn, and the subject is required to reproduce it immediately on a peace of paper (Administration A). The response is scored as correct, if all the figures, their size, shape and their spatial inter-relationships correctly reproduce the original design.

Dependent variable:

The dependent variable is the total number of pictures reproduced without errors. The scores range between 0 and 10, with higher score indicating better performance.

Fulfilment of the selection criteria:

BVRT is a popular test in clinical setting (Spreen and Strauss, 1998), but has not been used as widely as Visual Reproduction subtest of WMS-III in examining visual memory in schizophrenia. However, BVRT was considered more suitable for the purposes of the present investigation, because it contains three alternative forms (C, D, and E) of equivalent difficulty (Benton, 1972), making it ideal psychometrically for the repeated administration. Although not used extensively, BVRT has reliably produced deficient performance in schizophrenia patients (e.g. DeLisi et al., 1991a; Hoff et al., 1992; Silver and Geraisy, 1995; Silver and Shlomo et al., 2001). In a recent study (Rollnik et al., 2002) BVRT performance was found to improve with both typical and atypical antipsychotics, indicating that the test might be sensitive to antipsychotic treatment. (However, as no control group was used in that study, this improvement might be due to practice effect). Although BVRT has not been employed by any studies to date investigating the relationship between cognitive impairment and functional outcome, it was found to be predictive of facial emotion perception in chronic patients (Silver and

Shlomo, 2001), the deficit of which might have implications for social interaction and hence community outcome.

6.2.2.6. Verbal Learning and Memory

Hopkins Verbal Learning Test (HVLT-Revised, Shapiro et al., 1999)

Test description:

This measure is included to assess free recall – the index of declarative (explicit) memory. A subject is presented with a list of 12 nouns three times and the total number of words recalled after each presentation is recorded. The words comprising the list are drawn from three semantic categories (4 words for each category such as food, animals, tools, etc.). The task also allows testing recognition memory, but the score for recognition was not used in the present investigation, since recognition memory appears to be intact in schizophrenia patients (review, Sharma and Antonova, 2003).

Dependent variable:

The dependent variable is the total number of words recalled on three trials. The scores range between 0 and 36, with higher score indicating better performance.

Fulfilment of the selection criteria:

The HVLT is similar to the California Verbal Leaning Test (CVLT, Delis et al., 1987), which is widely used in schizophrenia research and in general clinical testing for the assessment of declarative memory. The HVLT was preferred to the CVLT due to the availability of six alternate versions, making it more suitable for the repeated testing. The paradigm inherent to both the HVLT and the CVLT has been very reliable in quantifying free recall impairment in first-episode and chronic schizophrenia patients (e.g. DeLisi et al., 1991a; Hoff et al., 1992; Kareken et al., 1996; Baare et al., 1999; Lysaker et al., 2000; Bilder et al., 2000). Conventional antipsychotics have been consistenly shown to impair free recall as measured by this paradigm, possibly due to their anticholinergic action and the need for anticholinergic medication to reduce EPS (review, Keefe et al., 1999). Atypcial antipsychotics, such as olanzapine, risperidone and quetiapine have been found to improve free recall as measured by the CVLT (review, Meltzer

and McGurk, 1999). Since the HVLT has similar psychometric properties, it was assumed that it would also be sensitive to potential improvement with atypical antipsychotic treatment in the present investigation. Verbal memory as measured by HVLT was found to positively associate with all measures of functional outcome assessed in the study by Velligan and colleagues (2000), including social and occupational functioning, level of independent living, work and productivity, and social competence.

Buschke Selective Reminding Test (BSRT, Buschke, 1973)

Test description:

This test was included to assess learning by means of measuring recall consistency. Recall consistency has been found to be very sensitive to anticholinergic effects (e.g. Thal and Fuld, 1983). The BSRT is a multi-trial list-learning test. After a list of 16 unrelated nouns has been presented to a subject and the subject has recalled as many words as possible, only the words that were not recalled on this trial are read to the subject on the next trial. On each trial the subject has to recall as many words as possible from the list, including the ones recalled on the previous trial. The test stops after 7 trials or after the subject has recalled all the words without a reminder.

Dependent Variable:

The BSRT allows calculating different indices of learning and memory, including total recall, long-term memory storage and retrieval, short-term retrieval, consistent long-term retrieval and random long-term retrieval. A single index may adequately quantify learning as measured by BSRT, given high intercorrelation of the scores and hence their redundancy (Spreen and Strauss, 1998). Westerveld et al. (1994) and Sass et al. (1994) have recommended the use of total number of words recalled on all trials as a measure of learning, since it is most reliable. Following this recommendation, the total number of words recalled was used as dependent variable to measure learning in the present investigation. The scores can range between 0 and 112, with higher score indicating better performance.

Fulfilment of the selection criteria:

The BSRT is one of the most widely used paradigms for assessing leaning and memory function following head injury (Spreen and Strauss, 1998), and is a

predictor of the overall level of disability 1 year after the injury (Levin et al., 1979). It has also proved useful in identifying children at risk for memory disorders (Snow et al., 1992). It is ideally suited for repeated testing as it contains alternate forms. BSRT has recently been employed in the schizophrenia research as a measure of learning producing impaired performance in patients (Sanfilipo et al., 2002). The effect of atypical antipsychotics on this test is not yet known.

In normal individuals, there appears to be a non-specific practice effect with repeated administration of alternate forms (Clodfelter et al., 1987; Hannay and Levin, 1985; Loring and Papanicolaou, 1987), which might reflect the ability to learn how to perform a complex task. Therefore, practice effect should be quantified and controlled for on this test.

Logical Memory (LM, WMS-III subtest, Wechsler, 1997)

Test description:

This test was used to assess memory for stories, both immediate and long-term. A subject is read two stories and asked to recall as many details of each story as possible immediately after presentation and then again 20 minutes after presentation.

Dependent variables:

Two dependent variables are derived by summing the total number of details recalled for both stories for immediate recall and long-term retention. Age scaled scores were derived from WMS-III manual. Aged scaled scores range between 1 and 19, with higher score indicating better performance.

Fulfilment of the selection criteria:

The LM test has been extensively employed in schizophrenia research and invariably revealed deficit in both immediate and delayed performance in fist episode and chronic patients (e.g. Saykin et al., 1991; Goldberg et al., 1994; Seidman et al., 1994; Kareken et al., 1995; Torres et al., 1997; DeLisi et al., 1997a; Levitt et al., 1999; Nestor et al., 2002; Toulopoulou et al., 2003) as well as in relatives of schizophrenia probands (Toulopoulou et al., 2003). Such an extensive interest in employing this task stems from the fact that memory for

stories might have more ecological validity in terms of community function, which is compromised in schizophrenia, than single word-list learning paradigms. Buchanan and colleagues (1994) observed a trend improvement on LM after 1-year treatment with clozapine (versus haloperidol), which was significantly positively associated with community outcome in patients.

The test-retest reliability coefficient of LM is sufficiently high (.71, Mittenberg et al., 1992) for repeated testing.

6.2.2.7. Verbal Fluency

Two aspects of verbal fluency, phonological and semantic, were assessed with letter and category verbal fluency tasks respectively (Milner, 1975). In letter fluency task, also known as FAS task, a subject is asked to produce as many words as possible starting from three letters: F, A, and S, excluding proper nouns, numbers, and the same word with a different suffix, and avoiding repetitions. Sixty seconds are given for responses for each letter. In category fluency task, a subject is asked to produce as many words belonging to three categories: animals, fruits and vegetables, avoiding repetitions. Sixty seconds are given for each category.

Dependent variables:

The dependent variables are the total number of words produced for three letters as a measure of phonological verbal fluency and the total number of words produced for three categories as a measure of semantic verbal fluency.

Fulfilment of the selection criteria:

Language skills in schizophrenia patients are most commonly assessed with verbal fluency tasks. Although many versions of the verbal fluency paradigm exist, the letter and category tasks selected are the most commonly used in both neuropsychological and neuroimaging investigations and are reliable in producing deficient performance in patients (e.g. DeLisi et al., 1991a; Bornstein et al., 1992; Vita et al., 1995; Baare et al., 1999; Sanfilipo et al., 2002). Verbal fluency as measured by category fluency task has been found to improve with clozapine (vs haloperidol) after 10-week of treatment, and to correlate with improved quality of life (Buchanan et al., 1994). Olanzapine, but not risperidone, has been

shown to produce improved performance on VF tasks (review, Meltzer and McGurk, 1999). Thus, VF tasks are sensitive to augmentation with atypical antipsychotics, although different brands might have differential effect.

Test-retest reliability is high (.88) after 19-42 days of testing in healthy adults (desRosiers and Kavanagh, 1987), indicating that the test is suitable for repeated testing. Short-term practice effects have not been previously reported (Spreen and Strauss, 1998).

6.2.2.8. Speed of Information Processing

Word Reading and Colour Naming parts of the Stroop task (Golden, 1978)

Test description:

The word reading and colour naming tests are control tasks of the Stoop test, which was described in the section 6.2.2.3 Attention. Word reading part involves reading colour words written in congruent colour ink as quickly as possible. Colour naming part involves naming the colour in which symbols XXXX are printed as quickly as possible. 45 seconds are given for each part.

Dependent variables:

Speed of word reading: the total number of words read in 45 seconds.
Speed of colour naming: the total number of colours named in 45 seconds.

Fulfilment of the selection criteria:

The use of performance on word and colour parts might be unorthodox in schizophrenia research and in general clinical testing, but there are good reasons for utilising these timed tasks as measures of speed of information processing in the present investigation. First, there is an inverse relationship between age and performance on Stroop word reading and colour naming parts in healthy adults attributed to age-related decline in processing speed (Uttl and Graf, 1997). Second, factor analytic studies (Graf et al., 1995) suggested that the speed of processing tasks (Digit Symbol) contribute to performance on Stroop colour naming part. Third, schizophrenia patients are known to perform significantly slower on both parts relative to healthy individuals (e.g. Hanes et al., 1996; Riley

et al., 2000; Krabbendam et al., 2000, 2001). Fourth, test-retest reliabilities of both parts are high, with the coefficient of .90 for the word reading and .83 for the colour naming (Spreen and Strauss, 1998). Finally, the utilisation of these tests, rather than the use of more common information processing speed measures, allowed keeping the number of the tests as low as possible to ensure reasonable administration time of the battery and hence optimal performance and low drop out rate.

6.2.2.9. Fine Motor Function

Finger Tapping Task (FTT, Halstead, 1947)

Test description:

This test assesses psychomotor speed by requiring the subject to tap on the leaver as quickly as possible with the index finger of the dominant hand and then non-dominant hand. Five 10-second trials are given for each hand. However, if the performance is inconsistent, deviating by more than 5 points on one or more trials, additional trials are given and the scores of the deviant trial(s) are discarded. A maximum of 10 trials is given for each hand.

Dependent variables:

Two dependent variables are computed representing the average number of taps from (the best) five trials for each hand.

Fulfilment of the selection criteria:

Finger tapping task is the most popular measure of psychomotor speed and is often used in clinical drug trials as well as structural imaging studies of schizophrenia patients. Due to the dopamine blockade in the basal ganglia, conventional antipsychotics impair psychomotor speed as measured by FTT (review, Medalia et al., 1988), whereas atypical antipsychotics spare it (review, Meltzer and McGurk, 1999).

Test-retest reliability was reported to be high for both dominant and non-dominant hands (.80) with minimal practice effects (Morrison et al., 1979), making the test suitable for repeated administration.

Grooved Peg Board Task *(GPB, Klove, 1974)*

Test description:

This test assesses dexterity by requiring a subject to fit metal grooved pegs into the holes as quickly as possible using dominant hand first and then non-dominant hand. The holes have a random arrangement with regards to the groove orientation, thus the subject's task is to rotate the peg first in order to make the groove fit the hole. Since the pegs are small and slime, this task requirement puts a considerable emphasis on the finger dexterity function. There are 25 holes in total arranged in 5 rows of 5 holes in each.

Dependent variables:

Two dependent variables are the time in seconds to complete the task for each hand.

Fulfilment of the selection criteria:

The GPB was selected since it is the most popular test of manual dexterity – a proxy for parkinsonism. Since dopamine blockade in the basal ganglia induces EPS, dexterity is affected in patients treated with conventional antipsychotics (Medalia et al., 1988). Dexterity as measured by the GPB was found to predict patients with rehabilitation potential (Weaver and Brooks, 1964). Spared or improved dexterity is, therefore, a desirable feature of pharmacological treatment with atypical antipsychotics. Further, dexterity as measured by GPB was found to be predictive of Performance subscale of WAIS (Schear and Sato, 1989), emphasising the importance of dexterity in general cognitive functioning. GBP has not been previously used in clinical trials of atypical antipsychotics.

Test-retest reliability for GPB is high (.79), although the practice effect is also significant (McCaffrey, Ortega, and Haase, 1993).

6.2.3. Procedures

The neuropsychological battery was administered to all participants, patients and controls, within a week of MRI scanning. The battery required approximately 1.5 hours for completion. Patients were allowed to take breaks as required to ensure optimal performance. The tests were administered in the following order:

National Adult Reading Test
Vocabulary sub-test of WAIS-III
Hopkins Verbal Learning Test
Buschke Selective Reminding Test
Finger Tapping Test
Trail Making Forms A, B
Continuous Performance Test
Wisconsin Card Sorting Test
Grooved Peg Board
Logical Memory-I (immediate)
Letter Verbal Fluency
Category Verbal Fluency
Letter-Number Test
Stroop Test
Benton Visual Retention Test
Logical Memory–II (delayed)*
* Or after 20 minutes if the tests following Logical Memory-I took longer than 20 minutes for completion.

For those tests with alternate forms (HVLT, BSRT, and BVRT), two different forms were administered to participants in each group in random order to counterbalance forms' presentation for repeated testing in Study 4. This was done to ensure that any changes in performance observed in Study 4 could not be attributed to the relative difficulty of the alternate forms.

To empirically validate the right-handedness of all participants, prior to the administration of the battery, hand preference was assessed using Edinburgh Handedness Inventory, shortened version (Oldfield, 1971). The total number of right- and left- hand items were scored, and the laterality quotient was computed as (total right-total left)/(total right + total left). Thus, laterality quotients could range from 1.00 (all items right) to –1.00 (all items left). Laterality quotient greater than .70 was taken to indicate strong right-hand preference.

6.2.4. Data Analysis

6.2.4.1. Preliminary Data Screening

Prior to the analysis, each variable was screened for missing values. Further, the variables were evaluated in relation to assumptions of the analysis of variance, i.e. the normality of distribution and the homogeneity of variance. The normality of distribution was assessed using the inspection of skewness (symmetry) and kurtosis (shape) coefficients as well as histograms with fitted normal curve and Q-Q plots. Whenever a variable severely deviated from being normally distributed, either *log* or *power* transformation was performed to remedy positive or negative skeweness respectively. The homogeneity of variance was evaluated using Error bar graphs representing standard deviations of two groups for each variable.

6.2.4.2. Standardisation

Due to the differences in scales of neuropsychological test scores, each variable was transformed using z-transformation (a scale with the mean of 0 and the standard deviation of 1) in order to evaluate relative impairment on different neuropsychological tests of patients against normal controls. The scores in both groups were standardised using control's mean and standard deviation for each variable.

6.2.4.3. Main analysis

A one-way analysis of covariance (ANCOVA), with group as a between-subject factor and neuropsychological variable as a within-subject factor, adjusting for the confounding effects of age and sex, was used to compare group differences for each neuropsychological variable. Since all neuropsychological tests employed in the study were hypothesised to produce impaired performance in the patient group, no adjustment was made for multiple comparisons. To assess a possible moderating effect of premorbid IQ, further ANCOVAS, adjusting for age, sex and NART score, were performed.

To investigate which of the neuropsychological variables best differentiated patients and controls, exploratory stepwise logistic regression (LR) with the diagnosis as a dependent variable and neuropsychological variables as predictors was performed, adjusting for gender, age, and premorbid IQ. LR does not require

the criteria of linearity, normality and the homogeneity of variance. It emphasizes the probability of a particular outcome for each case, given the person's pattern of responses on IVs. The outcome variable Y is the probability of having one outcome or another based on non-linear function of the linear combination of predictors. That is, the linear regression equitation is the natural log of the probability of being in one group divided by the probability of being in the other group. The maximum likelihood procedure is applied for the estimation of coefficients. The goal is to find the best linear combination of predicators to maximise the likelihood of obtaining the observed outcome frequencies.

6.3. Results

6.3.1. Preliminary Data Screening

Table 6.1. presents information on the missing values, outliers, skewness and kurtosis coefficients for each neuropsychological variable.

TABLE 6.1. Missing values, outliers, skewness and kurtosis coefficients for each neuropsychological variable by group

Dependent variable	Missing Data		Outliers*		Skewness#		Kurtosis$	
	Patients	Controls	Patients	Controls	Patients Statistic (se)	Controls Statistic (se)	Patients Statistic (se)	Controls Statistic (se)
NART IQ	1	-	-	-	-.247 (.357)	-.884 (.361)	-.634 (.702)	-.100 (.709)
WAIS-III IQ	-	-	-	-	.180 (.354)	.029 (.365)	-.291 (.695)	-.623 (.717)
HVLT total recall	2	-	-	-	.354 (.361)	-.323 (.361)	-.303 (.709)	-.725 (.709)
BSRT total recall	6	-	3[b]	1[a], 1[b]	.788 (.378)	.405 (.361)	.233 (.741)	1.323 (.709)
Finger Taping dominant	-	-	-	1[a]	-.426 (.354)	-.674 (.361)	-.659 (.695)	-.142 (.709)
Finger Taping non-dominant	-	-	1[a]	-	-.799 (.357)	-.333 (.361)	.215 (.702)	-.004 (.709)
Trail B-A	2	-	1[a]	3[a]	.152 (.357)	1.749 (.361)	3.336 (.702)	2.987 (.724)
CPT d'prime	2	1	-	-	.607 (.361)	.156 (.365)	-.190 (.709)	-.575 (.717)

GPB dominant	-	-	2[a]	1[b]	1.198 (.354)	3.026 (.361)	1.021 (.695)	4.204 (.709)
GPB non-dominant	-	-	4[a]	2[b]	1.132 (.354)	1.825 (.361)	.905 (.695)	5.047 (.709)
WCST perseverative responses	1	-	3[a]	2[a]	2.014 (.357)	2.752 (.361)	4.215 (.702)	9.922 (.709)
Logical Memory immediate	3	-	-	-	.611 (.365)	-.433 (.361)	.220 (.717)	-.338 (.709)
Logical Memory delayed	3	-	-	-	.253 (.365)	-.453 (.361)	-.461 (.717)	1.564 (.709)
Verbal Fluency letter	1	-	-	1[b]	.462 (.357)	.645 (.361)	-.184 (.702)	1.937 (.709)
Verbal Fluency category	1	-	-	-	.152 (.357)	-.724 (.361)	-.394 (.702)	.128 (.709)
Letter-Number correct	2	-	-	-	.358 (.361)	-.143 (.361)	-.337 (.709)	-.388 (.709)
Stroop word reading	3	2	-	-	.234 (.354)	.359 (.695)	.278 (.361)	.201 (.709)
Stroop colour naming	3	2	-	-	.532 (.354)	1.781 (.695)	-.593 (.361)	-.257 (.709)
Stroop interference score	3	2	-	-	.726 (.365)	.342 (.369)	.154 (.717)	-.144 (.724)
BVRT number correct	-	-	-	1[a]	-.021 (.354)	-1.213 (.695)	-1.028 (.361)	1.937 (.709)

* Number of extreme cases outside of the range defined by a minimum score: Lower quartile – 1.5 times inter quartile range, and a maximum score: Upper quartile + 1.5 times inter quartile range.

[#] A measure of the symmetry of the distribution. The value of zero indicates normal distribution. High positive value indicates a long right tail of the distribution. High negative value indicates a long left tail of the distribution. As a rough guide, skewness value more than twice its standard error is taken to indicate a departure from symmetry.

[$] A measure of the extent to which observations cluster around a central point. For a normal distribution, the value of the kurtosis statistic is 0. Positive kurtosis indicates that the observations cluster more and have longer tails than those in the normal distribution and negative kurtosis indicates the observations cluster less and have shorter tails.

[a] Low performance extreme

[b] High performance extreme

Abbreviations: se – standard error

NART-R IQ

There was one missing data value for a female first episode patient on NART due to dyslexia. Patients' NART IQ scores were normally distributed, whereas scores for normal controls were negatively skewed [skewness=-.884, se= .361]. This effect in the controls is due to the limited range of scores on the NART, which does not allow proper IQ estimation at the higher end of the distribution. No

transformation was performed, since the deviation from normality was not considered to be severe enough to invalidate the analysis of variance and was due to the psychometric weakness of the test, rather than deviant scores.

WAIS-III full scale IQ

There were no missing values for the WAIS-III IQ scale. Scores for both patients and controls were normally distributed, with similar variance.

HVLT

Two chronic patients attempted but could not complete HVLT. Their cases were treated as missing values in all analyses. *Free recall* scores for the remaining patients (n=43) and controls were normally distributed.

BSRT

Six chronic patients either refused or were unable to complete BSRT test. These cases will be treated as missing values in all subsequent analyses. There were three low performing outliers in patients' group and one low and one high performing outliers in the control group. However, since all outlier scores fell within the normal range of performance on this task, *free recall scores* for patients and controls were considered normally distributed, with comparable variance.

Finger Tapping Task

There were no missing values on FTT. *Dominant hand* scores were relatively normally distributed in both groups. An extremely high score [more than 1.5 interquartile range from the upper quartile], indicating poor performance, existed in the control group, but as the score was within the normal population range of performance on this task, the outlier was not excluded from the subsequent analyses. *Non-dominant hand* scores were reasonably normally distributed in both groups. However, skewness coefficient of patients scores [skewness=-.799, se=-.357] suggests negative skewness, but since the kurtosis coefficient [kurtosis=.215, se=-.004) and the inspection of the frequency histogram indicated that the shape of the distribution is near normal, the variable was not considered to violate the normality assumption.

Trail Task, part B-A

There were two missing values for TTT B-A score, due to inability to complete part B by two chronic patients. These cases were treated as missing values in all

analyses. There was one low performing outlier in the patient group, and three low performing outliers in the control group, but these scores were within the normal range of performance on this test. Skewness coefficient suggested severe positive skeweness in control group [skewness=3.336, se=.702]. The inspection of the boxplots and frequency histograms revealed that controls' score distribution was genuinely asymmetrical and might benefit from *log* transformation. *Log* transformation was therefore applied, which rendered the scores of both groups more normally distributed.

CPT-IP

There were two missing values in the patient group due to the inability to perform, with these cases excluded for the subsequent analyses of this variable. One missing value in the control group was due to the equipment failure and was substituted with the group mean, since the subject had an average performance on most other tests. Scores in both groups did not deviate from the normality assumption and had similar variances.

GPB

Scores for both dominant and non-dominant hands were positively skewed. Control group had an outlier. The scores of both groups were log transformed, which normalised the distribution and eliminated the outlier in the control group.

WCST

One patient refused to complete WCST; this case was treated as a missing value in all subsequent analyses of perseverative responses. Perseverative responses scores were severely positively skewed in both groups [Patients: skewness = 2.014, se = .357; Controls: skewness = 4.215, se = .702], with three under-performing outliers in the patients group and two in the control group. *Log* transformation has rendered the scores of both groups more normally distributed and eliminated the outliers. The variance was similar in two groups.

Logical Memory

Three chronic patients were unable to perform LM task, either immediate or delayed. Their cases were treated as missing values in all analyses of these variables. The scores for both LM immediate and delayed did not deviate from the assumptions of normality and homogeneity of variance in two groups.

Verbal Fluency

One patient refused to complete VF tasks. His case was treated as a missing value in all analyses involving letter and category VF scores. The remaining scores were normally distributed in two groups for both letter and category fluency, with similar variances. The test for outliers indicated a possible outlier in the control group for letter fluency, but since the score was within the normal performance range, it was not considered to disturb the homogeneity of the group.

Letter-Number Test

Two chronic patients were unable to perform on LNT. Their cases were treated as missing values in all analyses. The remaining scores were normally distributed in two groups, with similar variances.

Stroop Test

There were three missing values in the patient group and two in the control group due to the unavailability of the test form at the time of the assessment. The scores for these participants were interpolated from the scores of other participants with similar neuropsychological profile in their respective group. The scores for all three parts of the test were normally distributed in both groups, with similar variance.

6.3.2. Main Analysis

Table 6.2. presents means and standard deviations of the raw scores (unstandardised and untransformed), differences in z scores, F statistics, and p values for the differences in performance between patients and controls.

TABLE 6.2. Means and standard deviations of the raw scores, differences in z scores and the significance of these differences, adjusted for age and sex, for Premorbid IQ, Current IQ, and specific cognitive functions of patients and controls

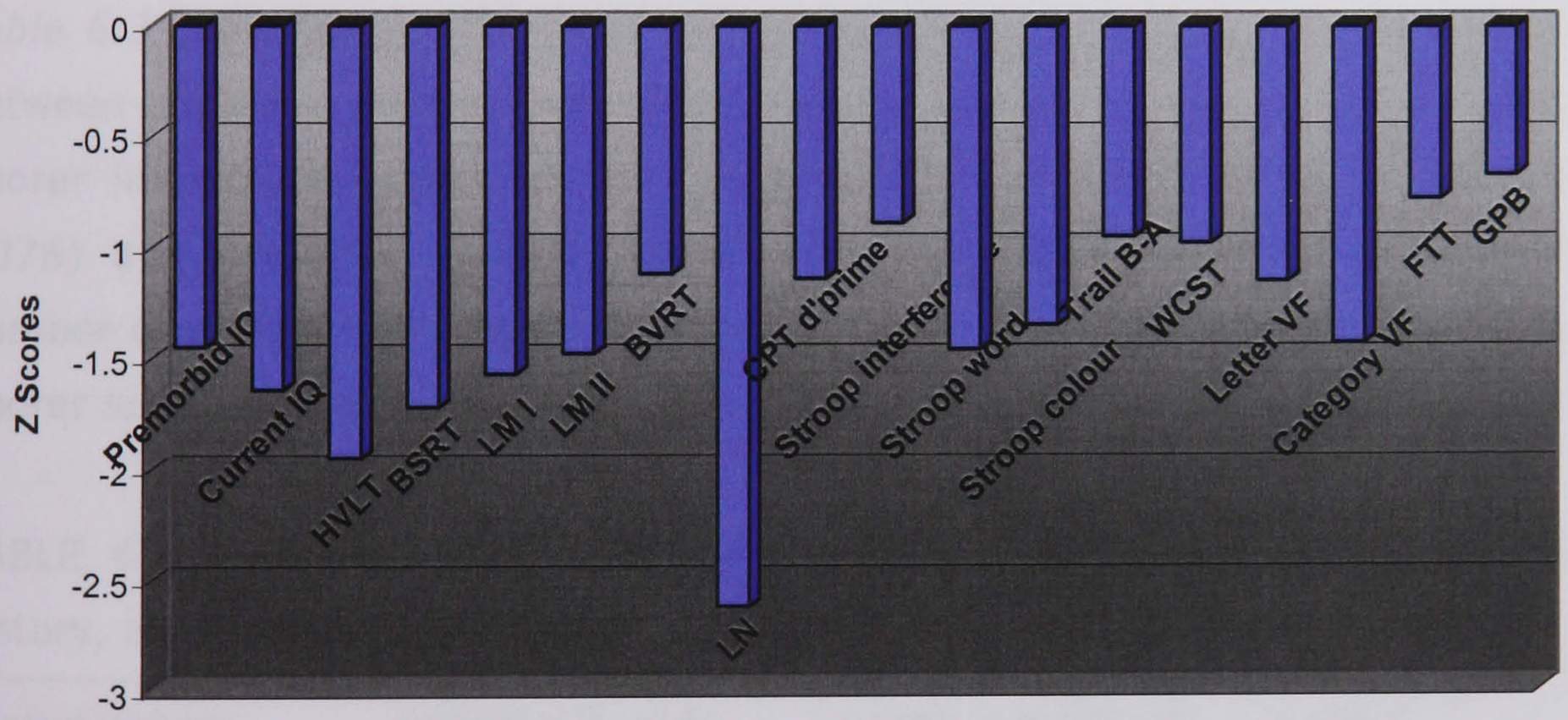
Dependent variable	**Patients**	**Controls**	**Analysis**		
	Mean (SD)	**Mean (SD)**	**Difference in *z* scores**	**Statistic**	**P value**
Premorbid full scale IQ: NART	100.71 (13.59)	114.44 (9.47)	-1.45	$F_{1,83} = 30.24$	<.0001
Current full scale IQ: WAIS-III	83.24 (16.46)	112.12 (17.55)	-1.64	$F_{1,84} = 55.95$	<.0001

Immediate verbal memory:					
HVLT free recall	17.26 (5.89)	26.79 (4.89)	-1.95	$F_{1,82}$ = 56.50	<.0001
Immediate visuo-spatial memory:					
BVRT number correct	4.73 (2.30)	7.05 (2.07)	-1.12	$F_{1,84}$ = 16.38	<.0001
Verbal Learning:					
BSRT total words recalled	42.28 (15.57)	71.05 (16.65)	-1.72	$F_{1,78}$ = 54.02	<.0001
Memory for Stories:					
Logical Memory immediate	7.98 (3.56)	13.51 (3.53)	-1.57	$F_{1,81}$ = 42.83	<.0001
Logical Memory delayed	6.45 (3.78)	11.186 (3.19)	-1.48	$F_{1,81}$ = 36.45	<.0001
Verbal Working Memory:					
Letter-Number total correct	8.33 (4.41)	16.40 (1.70)	-2.62	$F_{1,84}$=128.48	<.0001
Sustained Attention: CPT d'prime	.55 (.44)	1.57 (.90)	-1.14	$F_{1,82}$ = 38.31	<.0001
Inhibition (Selective Attention):					
Stroop interference score	-2.11 (8.67)	5.95 (9.07)	-.889	$F_{1,84}$ = 11.88	<.001
Speed of word naming:					
Stroop word score	84 (17.03)	105 (14.45)	-1.46	$F_{1,84}$ = 30.47	<.0001
Speed of colour naming:					
Stroop colour score	55 (12.55)	78 (16.79)	-1.35	$F_{1,84}$ = 44.54	<.0001
Mental Flexibility*:* Trail B-A*	57.79 (30.49)	36.12 (26.13)	.95	$F_{1,82}$ = 16.64	<.0001
Set-shifting (Perseveration):					
WCST perseverative responses *	28.11 (25.65)	13.40 (14.88)	.98	$F_{1,83}$ = 16.38	<.0001
Verbal Fluency:					
Phonological	30.39 (9.99)	44.23 (3.19)	-1.15	$F_{1,83}$ = 27.92	<.0001
Semantic	36.93 (9.95)	48.40 (12.01)	-1.43	$F_{1,83}$ = 28.01	<.0001
Psychomotor Speed and Dexterity:					
Finger Taping mean	41.30 (10.33)	48.51 (9.29)	-.78	$F_{1,84}$ = 10.70	<.002
GPB mean*	106.02 (47.79)	64.79 (10.21)	.67	$F_{1,84}$ = 18.95	<.0001

* Higher score indicates poorer performance

Patients' mean premorbid IQ was 1.45 standard deviations (sd) and current IQ was 1.64 sd below normal controls' mean [p < .0001]. Paired-samples t-test showed that patients' current IQ was significantly lower than their premorbid IQ [Premorbid IQ mean = 100.71, sd = 13.59; Current IQ mean = 83.24, sd = 16.46; t = 12.566, df = 43; p<.0001]. In addition to lower IQ, patients were significantly impaired on all cognitive functions, with deficits ranging from .67 to 2.62 sd relative to normal mean [*p* ranging from .002 to .00001, after adjusting for age and sex]. The average degree of impairment on neuropsychological measures was 1.30 standard deviation below the controls' mean. The severest deficits [difference in z scores greater than 1.5 sd] were observed for verbal working memory, verbal memory and learning, and memory for stories, both immediate and delayed, whereas psychomotor speed and dexterity were the least impaired (See *Figure 6.1* demonstrating the relative impairment on different measures).

FIGURE 6.1. Deficits in scores for premorbid IQ, current IQ, and specific cognitive abilities in patients relative to normal controls*



* By the definition of z-transformation, the control group has a mean score of zero on each measure.

ABBREVIATIONS: BVRT = Benton Visual Retention Test; FTT = Finger Tapping Test; GPB = Grooved Peg Board; HVLT=Hopkins Verbal Learning Test; LM I = Logical Memory immediate; LM II = Logical Memory delayed; LN = Letter-Number test; VF = Verbal Fluency; WCST = Wisconsin Card Sorting Test.

Since patients had significantly lower premorbid IQ, the influence of IQ level on other cognitive abilities was evaluated. Using ANCOVA, premorbid IQ did not have any effect on Buschke Selective Reminding Test free recall or Stroop interference score. It had some effect on immediate and delayed Logical Memory, Hopkins Verbal Learning Test total recall, Letter-Number task, Continuous

Performance Test d'prime, Wisconsin Card Sorting Test perseverative responses, Stroop word and colour naming, Trail Making form B-A, as well as phonological and semantic Verbal Fluency, but the difference on these tests was still significant between groups. The deficits in Finger Tapping, Grooved Peg Board and Benton Visual Retention Test performance could be completely explained by lower premorbid IQ in patients.

6.3.3. Relationships Between Cognitive Deficits and Clinical History

The relationships between cognitive deficits and clinical history, such as age of onset, duration of illness, and number of previous episodes and hospitalisations were investigated using partial correlations. The correlations of cognitive deficits with medical history variables were controlled for sex, since women are known to have later age of onset than men and tend to have less recurrent form of the illness (*Chapter 1*). Additionally, correlations between cognitive deficits and duration of illness, number of previous episodes and hospitalisations were controlled for age, since these variables are related to age.

Table 6.3 presents partial correlation coefficients for the significant relationship between cognitive deficits and clinical history. Earlier age of onset correlated with poorer immediate verbal memory (.323), and fine motor function, both speed (.376) and dexterity (-.385). There were trend associations between greater number of previous psychotic episodes and poorer cognitive flexibility (.311) and poorer semantic verbal fluency (-.300).

TABLE 6.3. Partial *r* correlation coefficients of cognitive deficits with clinical history, adjusted for age and sex

Clinical History	**Cognitive Deficits**	**Partial *r* coefficient (df)**	***p* value**
Age of Onset	HVLT total recalled	.323 (40)	.037
	FT mean	.376 (42)	.012
	GPB mean*	-.385 (42)	.010
Number of episodes	Trail B-A*	.311 (37)	.054
	Semantic VF	-.300 (38)	.06

* Greater score means poorer performance

In addition, patients with family history of schizophrenia had poorer psychomotor speed relative to patients with no family history [$t_{(38)} = 2.39$, $p = .022$], with the trend for significance remaining after controlling for age and sex [$p = .07$].

6.3.4. Relationships Between Cognitive Deficits and Symptoms

Partial correlations, adjusting for age and sex, revealed significant associations between poorer immediate verbal memory (HVLT total recalled) and greater severity of negative symptoms (-.418, df = 38, p = .009; individual items included blunt affect, poor rapport, and stereotyped thinking, $p < .05$); and poorer inhibition (Stroop interferences) and greater severity of general psychopathology (-.436, df = 39, p = .004; individual items included motor retardation, uncooperativeness, unusual thought content, poor attention, disturbance of volition, poor impulse control, active social avoidance, $p<.05$) as measured by PANSS.

6.3.5. Relationships Between Cognitive Deficits and Medication

Since high doses of typical antipsychotics and anticholinergic drugs are known to affect memory and psychomotor function, the degree of impairment on cognitive measures tapping memory and motor processes were investigated in relation to the current dosages of neuroleptic and anticholinergic medications. There were no significant relationship, but trend associations were observed between higher current neuroleptic dose and poorer logical memory, immediate (-.329, df = 27, p = .081) and delayed (-.315, df = 33, p =. 096).

In addition, patients who were on anticholinergic medication had significantly poorer speed of information processing, including Stroop word reading [$F_{(1.36)} = 11.984$, $p = .001$] and Stroop colour naming tasks [$F_{(1.36)} = 8.684$, $p = .006$], controlling for age and sex.

6.3.6. Exploratory Analysis

Stepwise logistic regression was performed to determine neuropsychological variables that had unique variance in classifying patients and controls into groups. Gender, age, and premorbid IQ were treated as covariates and were entered into the model using forced entry method. All neuropsychological

variables were entered into the model in a stepwise fashion using the forward maximum likelihood-ratio procedure. Due to the missing data, total of 33 patients and 43 controls were included in the analysis. The model with the best fit had three significant predictors: Buschke Selective Reminding Test, Letter-Number test, and Stroop colour naming, which correctly predicted 31 of 33 patients (93.9%) and 41 of 43 controls (95.3%) (see *Table 6.4*).

TABLE 6.4. The results of the stepwise logistic regression identifying neuropsychological measures with unique variance in predicting the schizophrenia diagnosis

Block	Method	Step	Independent Variable	Selected Model (Overall model statistics)						Final Model (Independent variable statistics)			
				-2 Log LR	Nagelkerke R^2	Change in −2 Log LR from prior step X^2	*p* value	Ration of correct predictions in classification		*Wald*	*p* value	*Exp (B)*	95% CI for *Exp (B)*
								SP	NC				
0		0	Constant							1.308	.253	1.303	
1	Forced (Enter	1	Gender	78.817	.379	...	...	22/33	37/43	.018	.893	.927	.306-2.807
			Age							5.247	.022	.950	.910-.993
			NART							13.579	.0002	1.101	1.046-1.159
2	Stepwise	1	Letter-Number	45.233	.723	33.584	.0006	28/33	41/43	15.064	.0001	7.042	2.628-18.869
	Stepwise	2	Letter-Number	39.125	.770	6.108	.0001	29/33	40/43	10.674	.001	6.066	2.111-17.619
			Stroop colour							5.249	.022	3.979	1.221-12.968
		3	BSRT	34.705	.803	4.420	.0005	31/33	41/43	3.741	.053	2.594	.987-6.819
			Letter-Number							6.375	.012	5.457	1.462-20.374
			Stroop colour							5.181	0.23	4.372	1.227-15.574

Model statistics:

−2 Log Likelihood Ration (LR) - a measure of how well the model fits the data, also called the deviance. *Change in −2 Log LR* tests the null hypothesis that the coefficients of the terms removed from the model are zero. Smaller value indicates better fit.

Nagelkerke R^2 - a generalised coefficient of determination, used to estimate the proportion of variance in the dependent variable which is explained by the predictor (independent) variables. It is based on the log likelihood for the model compared to the log likelihood for a baseline (i.e. constant only) model.

Wald's statistic – tests the significance of parameter estimates.

Exp (B) – e(2.718) raised to the value of the regression coefficient. This is the value by which the odds of the event change when the independent variable increases by one unit. If the value is greater than 1, the odds are increased; if the value is less than 1, the odds are decreased. A value of 1 leaves the odds unchanged.

95% C.I. (Confidence Interval) for Exp (B) – a range of values which N% of the time includes the value of e(2.718) raised to the parameter value.

6.4. Discussion

The aim of the present study was to quantify neuropsychological deficits in schizophrenia patients on the cognitive domains that have been consistently found to be compromised in schizophrenia and shown to bare significance for functional outcome. The neuropsychological measures were chosen for their reliability in differentiating patients and healthy controls in previous research. Consequently, patients were found to have impaired performance on all neuropsychological measures selected for the present investigation.

The deficits ranged from .63 standard deviations below the normal mean for dexterity to 2.62 standard deviations for verbal working memory. The greatest deficits (quantified as being greater than 1.5 sd) were observed on the measures of memory requiring verbal processing, including verbal working memory, immediate verbal memory and learning, and memory for stories, both immediate and delayed. The severity of these deficits was disproportional to the lower premorbid IQ levels of patients. Numerous other studies have observed differential impairment of these cognitive domains in schizophrenia patients, both chronic and first episode (reviews, Goldberg and Gold, 1995; Kuperberg and Heckers, 2000; Gur et al., 2000; Sharma and Antonova, 2003). Attention, visuo-spatial memory, and executive function showed a moderate impairment. Attention and executive dysfunction could only in part be explained by IQ deficits, whereas visuo-spatial memory impairment could be completely accounted for by IQ levels. In line with previous research (Hutton et al., 1998; Riley et al., 2000), the impairment of semantic verbal fluency was more pronounced than that of phonological verbal fluency and approached the criterion of a specific impairment (1.43 sd below the normal mean). Patients also showed considerable slowing on the speed of word reading (1.46 sd) and colour naming (1.35 sd) as measured by the control tasks of the Stoop test. Finally, fine motor dysfunction showed least impairment, which could be completely explained by IQ deficits. This relationship between psychomotor function and general intellegince is interesting, considering that psychomotor dysfunction is evident very early in life and is one of the most robust childhood predictors of adult schizophrenia (see *Chapter 2*). Rosenbaum and colleagues (2001) recently reviewed how intellectual and motor skills are acquired in fundamentally similar ways and concluded that basic coordination and timing processes seem to be required for interellectual as well as

motor skills. Therefore, the association between fine motor functioning and IQ levels in schizophrenia patiens might be explained by the parallel development of these processes early in life.

LNT, BSRT, and Stroop colour naming had a unique variance in predicting patients' group membership, indicating that the impairment in verbal working memory, verbal learning, and the speed of information processing were the 'signatures' of schizophrenia patients' neuropsychological profile relative to healthy individuals.

Schizophrenia patients as a group had an average premorbid IQ (normal population average is a score of 100 on the NART IQ scale). However, the findings of the present study indicate that this average score might not reflect the 'true' potential, yielding support for the notion of impaired premorbid IQ in schizophrenia. As has been noted in the introduction, IQ is best predicted from the parental SES. Patients had significantly lower premorbid IQ then would be expected from their parental SES, since patients and controls were matched on parental SES for the present investigation. These findings suggest that IQ impairment might be indicative of the disease process early in life and might be a risk factor for schizophrenia. Further, current IQ as measured by the Vocabulary sub-test of WAIS-III was significantly lower in patients than their premorbid IQ as measured by NART-R, suggesting that there might be a further IQ decline associated with the disease progression. However, it is known that NART-R tends to overestimate IQ at the lower end of the distribution (Nelson and Willison, 1991). Therefore, the difference between current and premorbid IQ scores in the patient group might reflect psychometric properties of the NART-R. Russell and colleagues (2000) have found that the NART overestimates premorbid IQ by an average of 15 IQ points, with about 10 points for 100-114 IQ band. In the present study, patients' current IQ was 17 points lower than their premorbid IQ. Further, controls' IQ scores fell within the 10-point over-estimation band of 100-114 score, but their scores on the measures of premorbid and current IQ are separated by an average of 2 points only. Thus, the difference in premorbid and current IQ scores in the patient group is unlikely to be completely explained by the psychometric limitations of the NART.

There were a number of associations between cognitive deficits and clinical characteristics. Poorer immediate verbal memory as measured by HVLT was

associated with earlier age of onset and greater severity of negative symptoms. This finding replicates that of Paulsen and co-workers (1995) who observed associations between CVLT, which is similar in its cognitive demands to HVLT, and age of onset and negative symptoms in schizophrenia patients. Greater severity of fine motor function was also associated with earlier age of onset. In addition, poorer psychomotor speed distinguished patients with familial history of schizophrenia spectrum disorders. In the recent review of 16 high-risk (HR) studies, which followed up longitudinally children at high-risk for schizophrenia (i.e. at least one parent diagnosed with schizophrenia spectrum disorder), Niemi and colleagues (2003) concluded that problems in motor function and verbal immediate memory (as well as attention) were predictive of schizophrenia later in life. For example, in the New York HR study, verbal immediate memory deficits predicted 83% of the HR offsprings who developed schizophrenia-related psychosis (Erlenmeyer-Kimling and Cornblatt, 1992; Erlenmeyer-Kimling et al., 2000). Recent report from the Edinburgh HR study of neuropsychological change in young people at HR for schizophrenia during a 2-year period indicated that decline in IQ and verbal memory preceded the development of psychotic symptoms. Taken together, the present findings and the findings of the previous studies suggest that deficits in verbal immediate memory and motor function play a role in pathogenesis of schizophrenia. Duration of illness did not associate with any of the cognitive deficits. This finding is in agreement with the longitudinal literature (review Rund 1998; Weickert and Goldberg 2000; Lewis, 2004) of the course and stability of cognitive deficits in schizophrenia, showing that there is no worsening in cognitive functioning over time apart from normal effects of age. Finally, poorer inhibition of pre-potent response was associated with greater severity of general psychopathology, particularly strongly with motor retardation, uncooperativeness, unusual thought content, poor attention, disturbance of volition, poor impulse controls, and active social avoidance. These associations make good theoretical sense and suggest that social avoidance in schizophrenia might be underlined by a basic cognitive dysfunction of poor inhibition, which manifests as disturbances in motor, thinking and volitional processes.

As predicted, the severity of memory deficit in schizophrenia patients was associated with anticholinergic treatment. The association, however, was limited to memory for stories, with both immediate and delayed recall being worse in patients who were taking adjunct anticholinergic procyclidine than in patients who were only taking

antipsychotics. This finding adds to the weight of evidence for the memory impairing effect of procyclidine in schizophrenia (Frith, 1984; Medalia et al., 1988; Spohn and Strauss, 1989; Cassens et al., 1990; Kumari et al., 2003b; Ettinger et al., 2003).

To conclude, the present study confirmed the presence of generalised (IQ) and specific cognitive deficits in schizophrenia patients, including verbal working memory, learning and memory, executive function, sustained and selective attention, verbal fluency, speed of information processing, and fine motor function. The present findings suggest that deficits in verbal working memory and speed of information processing best differentiate patients from normal controls; whereas deficits in fine motor function and visuo-spatial immediate memory appear to be present due to low general intelligence of some patients. Finally, the findings highlight the need for better treatment in schizophrenia in order to avoid further impairment of verbal memory and learning due to the anticholinergic treatment necessary with conventional antipsychotics.

CHAPTER 7. RELATIONSHIP BETWEEN STRUCTURAL ALTERATIONS AND COGNITIVE DEFICITS IN SCHIZOPHRENIA

7.1. Introduction

With the advent of brain imaging techniques, it has become possible to investigate in *vivo* Kraepelin's idea that cognitive dysfunction in schizophrenia are the manifestation of the underlying brain pathology, by studying the relationship between structural brain alterations and cognitive deficits.

Chapter 2 presented a comprehensive review of the Region of Interest (ROI) studies investigating structure/neurocognition relationship in schizophrenia. One of the issues that have emerged from the review is that ROI studies did not always distinguish between two issues: volume/neurocognitive ability relationship vs. structural alteration/neurocognitive deficit relationship. In other words, the studies investigated the relationship between the volume of measured structures and cognitive deficits regardless of whether the volume was altered in patients relative to controls, making the implication of their findings for the relationship between structural pathology and cognitive dysfunction in schizophrenia unclear.

The associations between structural alterations and cognitive deficits identified by the ROI studies (review, Antonova et al (2004), see also Chapter 2 and *Appendix I*) included: (i) reduced total brain and grey matter volumes with low premorbid IQ (Zipursky et al., 1998), deficits in executive (Kareken et al., 1995; Sullivan et al., 1996) and psychomotor (Sullivan et al., 1996) functions, verbal memory (Gur et al., 1999), visuo-spatial memory (Kareken et al., 1995; Gur et al., 1999), and attention (Gur et al., 1999), (ii) reduced PFC grey matter volume with attention and memory dysfunction (Gur et al., 2000a); (iii) reduced hippocampal volume (Gur et al., 2000b) and increased cerebellar vermis white matter volume (Levitt et al., 1999) with

memory deficits; and finally (iv) reduced volume of left striatum and putamen/nucleus accumbens complex with abstraction/categorization deficits (Stratta et al., 1997). The only VBM study of structure/neurocognition relationship (Saldago-Pineda et al., 2003) has reported an association between reduced grey matter concentration of the thalamus, angular, supramarginal, inferior frontal, and postcentral gyri of the left hemisphere and sustained attention deficits in first episode schizophrenia patients, but not in healthy controls.

Out of 22 ROI studies with the control group, which performed correlations for both patients and controls, 12 observed substantial differences in the pattern of structure/neurocognition relationship between the groups (Hoff et al., 1992; Bornstein et al., 1992; Flaum et al., 1994; Kareken et al., 1995; Sullivan et al., 1996; DeLisi et al., 1997a; Baare et al., 1999; Levitt et al., 1999; Nopolous et al., 1999; Krabbendam et al., 2000; Sanfilipo et al., 2002, Szeszko et al., 2003), with some associations being specific to schizophrenia patients (i.e. not seen in controls), and others lacking in patients (i.e. observed in controls but not in patients). For example, Sanfilipo et al. (2002) have observed positive correlation between left and right hippocampal volume and verbal memory in schizophrenia, but an inverse correlation between right hippocampal volume and verbal memory in controls. On the other hand, patients lacked an association between hippocampus and verbal fluency observed in normal controls. Further, left and right PFC white matter volume, which was significantly reduced in patients, was associated with cognitive flexibility in schizophrenia patients, but not in controls. Zipursky et al. (1998) found significant correlations between grey matter volume and IQ (as measured by NART and Quick test) in first-episode patients in schizophrenia, but not in normal controls. Krabbendam and colleagues (2000) observed an association between parahippocampal volume and information processing speed in patients, but not in healthy controls, despite no difference in hippocampal volume between the groups. Scezsko and colleagues (2003) reported the lack of 'normal' association between larger cerebellar volume and global as well as executive, visuo-spatial, and memory functions in a cohort of first-episode patients. Baare and colleagues (1999) found relative prefrontal volumes to positively correlate with immediate recall on verbal and visual memory and semantic fluency in patients, and only delayed visual memory in controls. For the detailed findings of other studies see *Chapter 2*, *Table 2.1*.

Although many studies have observed differences in the pattern of correlations in patients and normal controls, only three (Flaum et al., 1994; Zipursky et al., 1998; Szeszko et al., 2003) have formally tested whether these differences significantly differentiated the groups. Flaum et al. (1994) found that the correlation between enlarged putamen and IQ in female patients was significantly stronger than the correlations between this structure and function in either normal controls or affected men, using Fisher z transformations (Fisher, 1921). Szeszko et al. (2003) tested the difference in the strength of correlation between cerebellar volume and global functioning using non-transformed z score difference between two correlation coefficients and reported significantly stronger correlation in controls than in patients. Finally, Zipursky et al. (1998) found significant diagnosis-by-IQ tests interactions on grey matter volume using ANOVA, suggesting that the relationship between grey matter volume and general intellectual functioning is substantially different in patients relative to controls.

It is currently unclear whether these differences pertain to statistical artefacts, such as different range of structural volumes and neuropsychological performance resulting in different correlation strength, or whether they reflect altered structure/neurocognition relationship in schizophrenia, or perhaps both hold true in different cases (Antonova et al, 2004) *Appendix I*).

The present study investigated whether global and regional structural alterations identified in Study 1 (Chapter 5) are associated with impaired IQ and cognitive deficits of immediate and long-term verbal memory and learning, verbal working memory, immediate visuo-spatial memory, attention, executive function, verbal fluency, speed of word and colour naming, and psychomotor speed and dexterity observed in Study 2 (Chapter 6). Further, the study aimed to test explicitly and formally the hypothesis that structure/neurocognition relationship is altered in schizophrenia, such that some associations would be specific to patients, whereas others would be lacking relative to healthy individuals, with these differences not simply being due to statistical artefacts. Therefore, the study presents the following methodological advances relative to previous research: (i) the use of VBM for its power to identify structural alterations throughout the whole brain; (ii) investigating

strictly structural alteration/cognitive deficit relationship; (iii) explicit and formal testing of the altered structure/neurocognition relationship in schizophrenia, suggested by previous studies; and (iv) exploring possible statistical reasons for the differences in structure/neurocognition associations between patients and normal controls by comparing variance of two groups on both sets of variables, structural and neuropsychological.

Based on the previous literature reviewed above and in *Chapter 2*, it was predicted that reduced whole brain volume would be associated with impaired IQ and IQ-dependent cognitive abilities, including psychomotor speed (finger tapping) and dexterity (grooved peg board) (see Study 2, *Chapter 6*). These associations are likely to be due to the associations of these cognitive abilities with the grey rather than white matter volume. Specific regional alterations were predicted to be associated with specific cognitive deficits, independent of IQ. The IFG volume reduction was predicted to be associated with the deficits of verbal learning and memory, verbal fluency and sustained attention. The STG reduction was not found to associate with specific cognitive deficits in schizophrenia patients previously (Sanfilipo et al., 2002; Gur et al., 2000b), despite correlating with processing speed (Sanfilipo et al., 2002), spatial memory and attention (Gur et al., 2000b) in normal controls. Therefore, no relationship between STG reduction and cognitive deficits in patients was predicted. Enlarged putamen was found to associate with better WCST performance in chronic patients (Stratta et al., 1997). Therefore, it was predicted that enlarged putamen would associate with better WCST performance as measured by perseverative responses. The alterations of primary visual cortex, superior fascicules longitudinalis (SFL) and precuneus have not been studied previously in relation to cognitive deficits in schizophrenia. Based on the anatomical connectivity of these regions and their known functions from lesion and fMRI research, it was anticipated that LG grey and white matter reductions would be associated with impaired performance on measures involving visual processing, particularly with the timed component, including Benton Visual Retention Test and Stroop word reading and colour naming. SFL reduction was predicted to associate with impaired performance on measures involving verbal functioning, since this association tract connects language areas of prefrontal, temporal, and parietal cortex and thus is most important for language. The precuneus is known to activate during semantic processing and episodic memory tasks, along with left IFG, in normal individuals

(reviews, Cabeza and Nyberg, 2000, Binder and Price, 2001). Therefore, the volume of precuneus was predicted to associate with the verbal learning and memory, but the direction of this association was left open. Finally, it was predicted that some structure/neurocognition relationships would be specific to patients, whereas others would be lacking in patients relative to normal controls.

7.2. Method

7.2.1. Participants

The information on patient and control groups is presented in Chapter 5.

7.2.2. Measures

7.2.2.1. Structural Variables

The predicted values (y' adjusted = y' fitted + error) for the percentage of total grey/white matter volume at the maxima voxel of all the regions of between-group differences that were extracted for each participant in Study 1 for the analyses of the inter-relationships between altered regions, as well as their relationship with clinical variables, were used for the investigation of structural alterations with cognitive deficits.

7.2.2.2. Neuropsychological Variables

Since all neuropsychological measures were found to significantly differentiate patients and controls in Study 2, the standardised scores on all neuropsychological variables were used to investigate the relationship of structural alterations to cognitive deficits.

Data reduction techniques to reduce the number of neuropsychological variables for the investigation of structure/neurocognition relationships were not used for both theoretical and practical reasons. Theoretically, since the VBM method allows the identification of regional differences with high spatial precision, the use of factor scores or a priori scales might mask any potential associations between regional

structural alterations and cognitive deficits through the loss of measurement specificity of combinatory constructs such as factors and scales. Practically, data reduction techniques such as factor analysis could not be meaningfully applied due to the insufficient sample size as well as the lack of orthogonality between the factors when the procedure was attempted using the principal component analysis. To reduce the number of variables, the mean scores for two hands on Finger Tapping and Grooved Pegboard tasks were used since the scores for two hands were highly correlated ($r = .889$ and $r = .897$, $p <. 0001$).

7.2.3. Data Analysis

Partial correlations, adjusting for age and sex, were run in SPSS to investigate the relationship between structural and neuropsychological variables. This method was preferred to running correlations using VBM in SPM99 with small volume corrections (SVC) restricted to the regions found to be altered in patients relative to controls, because it allows deriving partial correlations coefficients for the association between structural and neuropsychological variables, which can be compared between the groups to investigate the issue of altered structure/cognition relationship in schizophrenia (see below). Moreover, two methods give similar results (as was ascertained by the present investigator), but the preferred one (i.e. using SPSS) is less computer intensive and time economical.

To minimize the chance of false positive errors due to the number of performed tests, the correlations were considered to be significant at $p <. 025$. Since the correlations between structural volumes and cognitive functions observed in ROI studies are modest (.350-.400 on average), more conservative *p* value would have substantially increased the risk of type II error.

Finally, to examine the issue of altered structure/neurocognition relationship in schizophrenia, partial correlations *r* coefficients, adjusted for age and sex, for each significant (at $p<.025$) structural predictor of a neuropsychological variable in patients or controls were compared with those of the other group using Fisher *z* transformations (Fisher, 1921). Fisher *z* transformation is applied to the test of a difference between two independent *r*s because when the population correlation coefficient ρ does not equal zero, the sampling distribution of *r* is not normal, and

becomes more and more skewed as ρ approaches ± 1, and its standard error is not easily estimated. The same holds true for the *difference* r_1 - r_2 (Howell, 1997).

Fisher (1921) showed that if *r* is transformed to

$$r' = (0.5)\log_e\left|\frac{1+r}{1-r}\right|$$

Then r' is approximately normally distributed around ρ' (the transformed value of ρ) with standard error

$$s_{r'} = \frac{1}{\sqrt{N-3}}$$

The null hypothesis that $\rho_1 - \rho_2 = 0$ is tested by converting each *r* to r' and solving for

$$z = \frac{r_1' - r_2'}{\sqrt{\frac{1}{N_1 - 3} + \frac{1}{N_2 - 3}}}$$

where *z* is the test statistic (*z* statistic is used rather than *t*, since the standard error does not rely on statistics computed from the sample and is therefore a parameter).

To ascertain the significance of *z* value at α = .05 two tailed, the following formula was applied in SPSS to calculate the p value:

p = (1-(CDFNORM(*z* value))*2

where 'CDFNORM' stands for the 'cumulative distribution function', which returns the probability that a random variable with mean of 0 and sd of 1 would be less than *z* value.

7.3. Results

7.3.1. Relationships between Structural Alterations and Cognitive Deficits in Patients

A number of structure/neurocognition associations were observed in patients, summarised in *Table 6,* presenting partial *r* coefficients for correlations between significant structural predictors and cognitive deficits in patients and partial *r* coefficients for the same pair of structure/neurocognition variables in controls, contrasted using Fisher *z* transformations to examine the specificity of these associations to schizophrenia. Reduced whole brain volume as well as white matter volume of the occipital lobe were associated with the deficit of phonological verbal fluency [r = 367, p<.023 , and r = .356, p <.023, respectively]. Reduced white matter of the occipital lobe was also associated with slower Stroop word reading [r = .437, p<.003] and colour naming [r = .483, p<.001]. Reduced total grey matter volume was associated with lower IQ [r = .397, p <.012] and impaired dexterity [r = -.382, p <.014]. Finally, enlarged precuneus was associated with better verbal learning as assessed by BSRT total words recalled [r = .395, p<.012]. Two of these structure/neurocognition associations significantly differentiated patients from controls, including those between larger precuneus and *better* verbal learning [p<.03]; and smaller OL white matter volume and poorer colour-naming speed [p<.01].

Re-examination of significant structure/cognition relationships in patients whilst controlling for premorbid IQ resulted in weakening or loss of the significance of the correlations between global volume measurements and cognitive deficits (i.e. WBV with GPB), whereas the correlations between regional grey and white matter alterations and cognitive deficits remained essentially unchanged.

7.3.2. Structure/Neurocognition Relationships Lacking in Patients

Partial correlations revealed a number of significant structure/neurocognition associations in controls that were either attenuated or completely absent in patients, including larger IFG with verbal learning [r=.391, p<.011], immediate memory of

stories [r=.358; p<.022], delayed memory for stories [r=.377, p<.015], and memory for visuo-spatial stimuli [.426; p<.006]; and smaller precuneus and better verbal working memory [r=-.454; p<.003]. The associations in controls differentiating them from patients most clearly were between IFG volume and verbal learning [p<.07], immediate memory for stories [p<.06], and visuo-spatial memory [p<.07], as well as precuneus volume and verbal working memory [p<.04]. (See *Table 7.1.* for the correlation coefficients in patients for the same pairs of structural/neurocognitive variables, and Fisher *z*-transformed values and the *p*-values for the between-group differences).

7.3.3. The comparison of variance on the structure/neurocognition pairs significantly differentiating the groups

The examination of the ranges for the variables constituting structure/neurocognition pairs that significantly differentiated patients and controls revealed similar variance in two groups on all pairs, except for GPB scores in patients which had greater variance than in controls, suggesting that the differences in the strengths of correlations on the same pairs of structure/neurocognition variables were not simply due to statistical artefacts.

TABLE 7.1. Partial correlations *r* coefficients, adjusted for age and sex, for the significant structural predictors of cognitive functions in (i) patients contrasted with the strength of the same relationships in controls (using Fisher *z* transformations); and (ii) controls contrasted with the strength of the same relationships in patients (using Fisher *z* transformations)

	Significant Correlations in Patients contrasted with Controls					**Significant Correlations in Controls Contrasted with Patients**				
Structural Variables	**Cognitive Variables**	**Patients**	**Controls**	**Z**	**p value**	**Cognitive Variables**	**Controls**	**Patients**	**z**	**p value**
Whole brain volume	VF phonological	.367*	.286	.40	.69	None	-	-	-	-
Total grey matter volume	NART	.397*	.320	.88	.38	None	-	-	-	-
	GPB mean	-.382*	-.009	1.79	.07					
Total white matter volume	None	-	-	-	-	None	-	-	-	-
Inferior Frontal Gyrus	None	-	-	-	-	BSRT total recall	.391*	.008	1.84	.07
						Logical Memory immediate	.358*	-.040	1.89	.06
						Logical Memory delayed	.377*	.050	1.32	.19
						BVRT number correct	.426*	.057	1.81	.07
Lingual Gyrus	None	-	-	-	-	None	-	-	-	-
Superior Temporal Gyrus (first voxel)	None	-	-	-	-	None	-	-	-	-
Superior Temporal Gyrus (second voxel)	None	-	-	-	-	None	-	-	-	-
Posterior Putamen	None	-	-	-	-	None	-	-	-	-
Precuneus	BSRT total recall	.395*	.025	2.13*	.03	Letter-Number correct	-.454**	-.032	2.09*	.04
Superior Fasciculus Longitudinalis	None	-	-	-	-	None	-	-	-	-
OL white matter	Stroop word	.437**	.103	1.65	.10	None	-	-	-	-
	Stroop color	.483**	-.071	2.71**	.01					

* Significant at the 0.025 level (2-tailed)

** Significant at the 0.01 level (2-tailed)

7.4. Discussion

Structural alterations were predictive of some cognitive functions in patients. As hypothesized, the indices of global brain tissue availability showed a non-specific relationship to cognition, with total grey matter associating with premorbid IQ and dexterity, which was dependent on premorbid IQ levels. In addition, whole brain volume positively correlated with phonological verbal fluency in patients. Controls showed similar pattern, except for the association between total grey matter volume and dexterity. Overall, there were no significant differences in the pattern of structure/neurocognition relationships between global brain tissue availability and premorbid IQ as well as IQ-dependent cognitive function between patients and controls, albeit controls showed somewhat weaker associations.

As predicted, the regional structural alterations were associated with specific cognitive functions in both groups. Further, supporting the prediction, some associations were specific to patients, whereas others were specific to controls. The clearest differentiation between two groups was observed for the relationships between regional structural volumes and learning and memory. In controls, IFG volume was associated with verbal and visuo-spatial memory, differentiating them from patients with 6% and 7% probability of this occurring by chance. In patients, enlarged precuneus was associated with *better* verbal learning, significantly differentiating them from controls (3% probability). Left IFG and precuneus are commonly activated during semantic processing and episodic memory tasks in normal individuals during fMRI experiments (reviews, Cabeza and Nyberg, 2000, Binder and Price, 2001). Left IFG (BA 45/47) is proposed to be involved in selecting, comparing, or deciding on information during mnemonic processes (Petrides, 1995). The precuneus, due to its proximity to the retrosplenial cortex (Vogt, 1976), which is richly connected with hippocampus, parahippocampus (Mufson and Pandya 1984; Suzuki and Amaral, 1994) and anterolaterodoral thalamus (Sripanidkulchai and Wyss, 1986), is proposed to play a role in episodic memory encoding (de Zubicaray et al., 1998; Capilotti and Macquire, 2003), retrieval (Buckner et al., 1996; Krause et al., 1999) and retrieval success (Kapur et al., 1995). Fletcher and colleagues (1995) suggested that the role of the precuneus in episodic memory is that of a 'mind's eye', imagining the learned episode, and showed that the precuneus activation was much stronger for imaginable than for non-imaginable words. Thus, left BA 45/47 and the precuneus are two nodes of the functional network involved in mnemonic processes. The findings of the present study suggest that greater

volume of left ventrolateral prefrontal cortex was a determinant of better performance on memory and learning tasks in normal controls. In the patients, on the other hand, the structural volume reduction of this region appears to have resulted in the loss of function, as evidenced by the observed differential deficit in memory and learning. The larger precuneus in some of the patients appears to have a beneficial effect on verbal learning and memory function. However, larger precuneus was also associated with greater number of psychotic episodes and hospitalizations in patients (Study 1, Chapter 5), suggesting that enlarged precuneus might have implications for schizophrenia course. Interestingly, in controls, larger precuneus was associated with poorer verbal working memory, suggesting that in healthy individuals larger precuneus might be detrimental for on-line cognitive information processing and manipulation. The putative enlargement of the precuneus and its implications for psychopathology and cognitive functioning in schizophrenia should be investigated further, as this area is largely unexplored in relation to schizophrenia as well as normal cognition. It would be interesting, for example, to investigate whether larger precuneus in healthy individuals is associated with the presence of schizotypal traits.

It is noteworthy that phonological verbal fluency performance did not associate with the IFG volume either in patients or controls, since BA 45/47 is commonly found to activate during performance on this task (e.g. Fiez, 1997; Weiss et al., 2003).

Other structure/function relationships that significantly differentiated patients from controls were that of the greater white matter volume reduction of the primary visual cortex and poorer speed of word and color naming. These associations suggest that deficits in word and color naming speed in patients might be due to the compromised function early in the brain's visual information processing hierarchy.

In line with the prediction, STG reduction did not associate with cognitive deficits in patients. There were no associations between STG volume and cognitive function in controls either. Although anticipated, this lack of relationships between STG volume and cognitive function in either group is somewhat surprising. Anterior temporal pole is associated with the semantic system function. Anterior temporal pole atrophy, especially on the left, is a hallmark of semantic dementia, as found by two VBM studies (Mummery et al., 1999; 2000). Functional imaging studies of normal controls show the activation in temporal operculum during the tasks requiring access to semantic knowledge (e.g. Demonet et al., 1992;

Mummery et al., 1996; Pugh et al., 1996; Vandenberghe et al., 1996). In line with this functional role, one ROI study has found smaller (but not reduced!) left STG volume to associate with poorer verbal fluency in schizophrenia patients (Vita et al., 1995). However, Sanfilipo et al. (2002) did not find such an association between *reduced* STG volume and differentially impaired verbal fluency. It is plausible, that, as in the case with IFG volume reduction, anterior STG reduction resulted in the loss of function, as evidenced by the differential impairment of semantic verbal fluency in patients, but no direct relationships are observable perhaps due to other mechanisms playing a greater role in the face of STG structural and functional disruption.

The most obvious limitation of this study is the number of performed tests without the correction for multiple comparisons, although the chance of false positives was minimized by adopting a more conservative *p* value of .025. The structure/function correlations that were observed in ROI studies are generally modest and rarely exceed 35%. Thus, such stringent corrections as Bonferroni method might result in multiple type II errors. Taken these limitations into account, the results of the present study should be considered as putative and are in need of a replication.

To conclude, the present study is the first to investigate, to the best of author's knowledge, the structure/neurocognition relationships in schizophrenia patients with optimized volumetric VBM approach and using a comprehensive neuropsychological battery. Further, it is the first study to explicitly test the hypothesis that structure/function relationship in schizophrenia might be altered. The results revealed left hemisphere localized structural alterations to associate with specific (not general) cognitive deficits in patients. Some structure/neurocognition associations appeared to be specific to schizophrenia, and some were lacking in patients relative to normal controls.

CHAPTER 8. STRUCTURAL ALTERATIONS AS PREDICTORS OF TREATMENT RESPONSE TO ATYPICAL ANTIPSYCHOTICS

8.1. Introduction

As has been reviewed in detail in *Chapter 3* of the General Introduction, atypical antipsychotics have greater efficacy than typical antipsychotics in improving cognitive deficits characteristic of schizophrenia. Three most commonly used atypical antipsychotics in clinical practice are *olanzapine*, *risperidone* and *quetiapine*. Although divergent in their broader pharmacological profile, all three drugs share one common property: serotonin-dopamine antagonism, which is, as discussed in *Chapter 3*, is thought to relate to their greater cognitive efficacy than typical neuroleptics, which are exclusive dopamine antagonists. The lack of need for anticholinergic medication as an adjunctive treatment with atypical antipsychotics may also contribute to better cognitive functioning of the patients taking atypical antipsychotics.

Earlier comparative studies of risperidone and olanzapine with small samples have suggested that these drugs might have differential effect on cognitive functioning (Cuesta et al., 2001, unpublished pilot study in Harvey et al., 2003). Purdon et al. (2000) with larger sample of patients (n = 65) have reported olanzapine to be superior to risperidone, but as argued by Sharma (2002), this differential effect might be due to unjustifiably high doses of risperidone used in the study. Most recent comparative studies with large sample sizes and clinically equivalent dosages did not support the notion of differential cognitive efficacy of olanzapine and risperidone, reporting no significant differences in the magnitude of produced improvement in cognitive functions (Bilder et al., 2002; Harvey et al., 2003). There are presently no published studies comparing quetiapine with other atypical antipsychotics in cognitive efficacy.

Patients with earlier onset schizophrenia have more marked structural brain alterations than adolescence- or adult- onset schizophrenia (review, Mehler and

Warnke, 2002). Earlier age of onset is also associated with poorer response to treatment (Metlzer et al., 1997) and higher dosage of typical antipsychotics (Dernovsek and Tavcar, 1999). The degree of enlargement of CSF spaces (Harvey et al., 1993; Knoll et al., 1998; Lieberman, 1999) and cortical volume reduction (Zipursky et al., 1998) were shown to relate to the rate of symptom response to typical antipsychotics. Similarly, prefrontal sulcal prominence (Friedman et al., 1991), temporal CSF volume (Lauriello et al., 1998), and DLPFC and TL grey matter volumes (Molina et al., 2003a) were found to predict responsiveness to clozapine in schizophrenia in terms of clinical improvement. Molina et al. (2003b), however, did not find the volumes of total CSF, DLPFC CSF and grey matter, TL CSF and grey matter, and hippocampus to be predictive of clinical symptom improvement with risperidone treatment. It has not been previously investigated whether basal structural volumes are predictive of the degree of cognitive improvement with atypical antipsychotics.

The present study, therefore, sought to investigate whether the degree of structural brain alterations is predictive of cognitive treatment response to atypical antipsychotics. To this end, cognitive functioning in patients on atypical antipsychotics (as one class of drugs) was compared with their cognitive functioning whilst on typical antipsychotics. In their review and meta-analysis of atypical antipsychotic trials, Keefe and colleagues (1999) recommended that the following conditions be met for a rigorous study comparing typical and atypical antispychotics: i) a within-subject design; ii) 4-to 6-week period of stable treatment with typical antipsychotics prior to the baseline assessment; iii) low dosages of typical antipsychotics as a comparator; iv) the assessment of positive and negative symotoms, as well as side effects and movement disorders at each neuropsychological assessment in order to discriminate between cognitive enhancement vs generalised clinical change. Following these recommendations, cognitive functioning in schizophrenia patients was assessed at two time points in a within-subject design: the baseline whilst the patients were treated with conventional medication for a period of at least 6 weeks, and after 6 weeks of treatment with one of the atypical antipsychotics, olanzapine, risperidone or quetiapine. Low dosages of typical antipsychotics were used as a comparator, and the assessments of overall clinical change in terms of symptoms, side-effects and movement disorder was carried out. A group of healthy individuals was included in order to control for the test-retest practice effects. It was hypothesised that patients would show significant improvement on neuropsychological test performance after 6-week treatment with atypical antipsychotics due to their shared property of dopamine-serotonin antagonism;

and that less altered structural volumes would be predictive of greater cognitive improvement.

8.2. Method

8.2.1. Design & Procedures

The study has a within-subject design with two groups: one experimental (schizophrenia patients switched from conventional to atypical antipsychotics), and one control (healthy volunteers). The control group was included to estimate normal practice effect on neuropsychological measures.

Each participant was tested on two occasions, the baseline (as described in Study 2) and after 6 weeks. After the baseline MRI and neuropsychological assessment, schizophrenia patients were randomly assigned to one of the three atypical antipsychotics: olanzapine, risperidone or quetiapine. Randomisation was undertaken in order to exclude clinical bias in switching patients to one of the three atypical antipsychotic.

8.2.1.1. Randomisation Procedure

Randomisation was achieved by creating a randomisation table, an excerpt of which is provided below (see *Table 8.1*). The table represented a matrix of gender by age with three different age groups: from 18 to 33; from 34 to 50; and from 51 to 65 years of age. Each medication type has been given a letter code, A, B, or C, and these letters were pseudo-randomised across the three age groups in the following way. The first letter sequence was A-B-C, followed by B-C-A, followed by C-A-B. These three sequences were repeated in this order across the age groups. The person responsible for randomisation was unaware of the results of initial screening and baseline clinical and neuropsychological assessment. The investigators responsible for assessments were unaware of the randomisation procedure. This was done in order to prevent potential biases at the assessment and assignment stages of the trial.

TABLE 8.1. Randomisation matrix for four experimental medication groups

MALE	**FEMALE**	
	AGE 18-33	
Name	Name	GROUP
1	1	A
2	2	B
3	3	C
4	4	B
5	5	C
6	6	A
...	...	...
	Age 34-50	
1	1	A
2	2	B
3	3	C
4	4	B
5	5	C
...	...	...
	Age 51-65	
1	1	A
2	2	B
3	3	C
4	4	B
...	...	...

8.2.1.2. Blinding

The study utilised a single-blind design where investigators responsible for clinical and neuropsychological assessments were blind to the atypical antipsychotic that the patients were treated with. Since there is a possibility of the differential effect of atypical antipsychotics on cognition, the blinding was implemented as a precautionary measure to exclude the possibility of the investigator bias during the assessments.

Patients were aware of the type of the medication they were receiving. Although this method might be open to criticism due to the possibility of patients' created biases in their responses during the neuropsychological assessments, these are improbable for the following reason. Even if the patients were knowledgeable in regard to cognitive effects of the atypical antipsychotic, the fact that patients were randomised after the baseline assessment prevents them from 'holding back' their responses at the baseline, and then 'improving' their performance at the follow up assessment, either consciously or unconsciously. Thus, if the atypical antipsychotics were to be found to improve neuropsychological performance from the baseline to 6-week assessment, this would be unlikely to arise due to the patients' created biases.

In regard to the assessment bias issue, the 'blinding' of investigators responsible for clinical and neuropsychological assessments is of a far greater importance and necessary measures were implemented to ensure that clinical and neuropsychological assessments were performed under the 'blind' conditions.

8.2.1.3. Dosage of Atypical Antipsychotics

Starting doses for atypical antipsychotics were according to the "Summary of Product characteristics" for each individual drug: 20 mg for olanzapine, 2 mg for risperidone, and 50 mg increasing to 400 mg over three-four days for quetiapine. Optimal dosage for each patient was achieved within 14 days after the switch and the patients were retested after having been on the optimal dose for 6 weeks.

8.2.1.4. Adjunctive Medication

Anticholinergic medication was permitted in the study if required together with atypical antipsychotic. This method was applied to avoid the increased EPS that may result from discontinuation of anticholinergic medication, which might have reflected poorly on cognitive performance at 6 weeks. Further, this method made the medication regime at 6 weeks comparable to the one during conventional antipsychotic treatment; and allowed measuring the effect of atypical antipsychotics above and beyond the effect of adjunctive anticholinergic medication. Finally, this method is more representative of actual clinical practice, which makes the findings of the present study directly applicable to clinical practice. Thus, this is an appropriate method to estimate the effects of atypical vs. conventional antipsychotics on cognitive functioning. However, every attempt was made to keep patients on monotherapy as far as possible.

8.2.1.5. Exclusion Criteria

Patients were excluded from the study if i) co-medication not allowed in the study was required for the patient along with psychotropic medication tested in the study (e.g. additional antipsychotic medication, mood stabilisers); ii) compliance with prescribed medication was lacking; or iii) no significant medication effect was ascertainable or serious adverse reaction to the medication had occurred (as judged by the treating physician).

8.2.2. Participants

PATIENTS: 30 (Male/Female = 20/10) out of 41 patients on conventional antipsychotics who were recruited for Studies 1, 2, and 3 (for sample details see Chapter 5: General Method) gave consent to participate in the study. Patients were told that they were to take part in the study of the effect of atypical antipsychotics on cognition, and that they would be randomly allocated to treatment with one of the novel antipsychotics: olanzapine, risperidone, or quetiapine; after which they were to repeat the neuropsychological assessment following 6 weeks of treatment. Patients were instructed that they could withdraw their consent at any time without having to provide a reason. Three patients (Male/Female = 2/1) allocated to atypical group withdrew their consent before they were switched. Two male patients switched to risperidone relapsed and were excluded from the study. Three patients (Male/Female = 2/1) patients switched to quetiapine required adjunctive depot medication due to the exacerbation of the symptoms and were consequently excluded from the study. Thus, 22 patients (Male/Female = 14/8) have constituted the experimental group: 9 (Male/Female = 6/3) patients on olanzapine, 6 (Male/Female = 4/2) patients on risperidone, and 7 (Male/Female = 4/3) patients on quetiapine.

Table 8.2 lists clinical characteristics of the patients, including diagnosis, illness type, familial history, age of onset, age of first hospitalisation, duration of illness, number of previous episodes and hospitalisation, and symptom ratings using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987).

CONTROLS: 25 individuals from the control group of Studies 1, 2, and 3 gave consent to participate in the study. 23 (Male/Female = 14/9) have completed the study, with two individuals withdrawing before 6 weeks assessment.

Table 8.3 presents demographic characteristics of the final sample. Two groups were matched on age, sex, ethnicity and parental SES. Normal controls had significantly higher levels of education than patients, as well as premorbid and current IQ ($p < .001$).

TABLE 8.2. Clinical characteristics of the patients

Characteristic	**Atypical (n=22)**
Diagnosis:	
Schizophrenia, paranoid	17
Schizophrenia, undifferentiated	2
Schizophrenia, residual	2
Schizoaffective disorder	1
Family history:	
Yes	8
No	14
	Mean (SD)
Age at onset of first symptoms:	20.72 (13.40)
Age at first hospitalisation:	25.95 (9.98)
Duration of illness (years):	14.68 (12.61)
Number of previous episodes:	3.80 (3.81)
Number of previous hospitalisations:	2.68 (2.55)
PANSS Positive symptoms:	17.5 (6.94)
PANSS Negative symptoms:	18.50 (9.38)
PANSS General Psychopathology:	37.64 (9.62)
Conventional antipsychotics dosage (CPZ equivalents mg)	255.88 (220.71)
Anticholinergic medication:	N=8
Dosage	4.81 (.99)

TABLE 8.3. Demographic characteristics of the final sample

Characteristic		**Atypical Group (N=22) Mean (SD)**	**Normal Control Group (N=23) Mean (SD)**	**Statistics**
Age		40.64 (12.46)	37.65 (13.24)	$T_{(43)}$ = .778; p=.441
Sex:	Male	14	14	$X^2_{(1)}$ = .037; p=.848
	Female	8	9	
Education		12.27 (3.60)	16.76 (3.98)	$T_{(43)}$ =-3.963; p=.0003
Premorbid IQ (NART)		105.23 (11.72)	116.04 (11.69)	$T_{(43)}$ = -3.099; p=.003
Current IQ (WAIS-III)		87.09 (14.60)	112.43 (21.54)	$T_{(43)}$ = -4.599; p<.0001
Ethnicity:	Caucasian	16	16	
	African	4	2	
	South-East Asian	2	2	$X^2_{(4)}$ = 3.646; p=.456
	Mixed Race	-	2	
	Other	-	1	

continued from p.205

Parental SES:			
Professional	2	3	
Intermediate	6	7	
Skilled: non-manual	-	2	$X^2_{(5)}$ = 8.627; p=.125
manual	6	3	
Semi-skilled manual	3	5	
Unskilled manual	4	3	

8.2.3. Measures

8.2.3.1. Structural Variables

The predicted values (y' adjusted = y' fitted + error) for the percentage of total grey/white matter volume at the maxima voxel of all the regions of between-group differences that were extracted for each participant in Study 1, were used to investigate the predictive validity of structural alterations in treatment response with atypical antipsychotics.

8.2.3.2. Neuropsychological Variables

Scores on the neuropsychological measures obtained in Study 2 were used as the baseline scores. The neuropsychological battery described in Study 2, excluding the measures of general intelligence, NART and Vocabulary sub-test of WAIS-III, was used to assess cognitive functioning at the 6-week assessment. Where available, alternate test forms were used at the follow-up assessment, including Hopkins Verbal Learning Test, Buschke Selective Reminding Test, and Benton Visual Retention Test. Alternate test forms were counterbalanced for the baseline and follow-up assessments.

8.2.3.3. Clinical Variables

PANSS (Kay et al., 1987) was re-administered by the qualified psychiatrists at the follow-up assessment in order to ascertain changes in symptomatology with atypical antipsychotics from baseline to 6 weeks of treatment.

In order to ascertain that cognitive change with atypical antipsychotics was not simply the result of reduced side effects induced by conventional antipsychotics, extrapyramidal, neurological, and autonomic side effects were assessed at the baseline and at 6 weeks using Simpson-Angus Rating Scale (SARS) for Extrapyramidal Side Effects (Simpson and Angus, 1970), Barnes Akathisia Scale

(BAS, Barnes, 1989), and Abnormal Involuntary Movement Scale (AIMS, Guy, 1976).

8.2.4. Statistical Analyses

8.2.4.1. Data Distribution

The raw scores on all the variables were checked for the normality of the distribution at the baseline and 6 weeks. Skewed variables were transformed in order to meet the requirements of parametric tests.

8.2.4.2. Missing Data

All variables were checked for missing values. Any cases with missing values were excluded from the analysis per variable.

8.2.4.3. Test-Retest Reliability of Neuropsychological Measures

Pearon's product moment correlations between the baseline and 6 week scores were used to investigate normal (i.e. using control group data) test-retest reliability of each neuropsychological measure.

8.2.4.4. Practice Effect

Paired-sample t-tests were used to investigate normal (i.e. using control group data) practice effect on each neuropsychological measure.

8.2.4.5. Effects of Atypical Antipsychotics on Cognitive Functioning

Due to the possibility of differential effects of three atypical antipsychotics on a given cognitive function, the statistical significance of the score change from baseline to 6 weeks was evaluated using a mixed-model analysis of variance (ANOVA), with time (baseline and 6 week scores) as the within-subject factor, and the atypical antipsychotic type (olanzapine, risperidone, or quetiapine) as the between-subject factor. Bonferroni correction was applied to adjust for the number of performed comparisons; therefore, the main effect of time was considered significant at $p<.003$ (α of .05/16 comparisons).

For those neuropsychological tests that showed significant improvement, a mixed-model ANOVA, with time (baseline vs. 6 weeks) as a within-subject factor, and group (patients vs. normal controls) as a between-subject factor, was used to ascertain whether the improvement observed in patients was significantly greater than what would be expected due to the normal practice effect. The results of time by group interaction were considered significant at 5% level.

8.2.4.6. Structural Predictors of Cognitive Improvement

Stepwise multiple linear regressions with the 6-week score as a dependent variable and the global and regional structural volumes as predictors were used to investigate whether any global or regional structural volumes were predictive of the 6-week score. The baseline score was entered into the model as a covariate (i.e. forced entry) to account for the effect of baseline performance on the follow up scores. Structural predictors were considered significant at 5% level.

8.2.4.7. Effects of Atypical Antipsychotics on Symptoms

A mixed-model analysis of variance (ANOVA), with time (baseline and 6 week scores) as the within-subject factor, and the atypical antipsychotic type (olanzapine, risperidone, or quetiapine) as the between-subject factor was used to investigate the significance of the effect of atypical antipsychotics as compared with conventional antipsychotics on positive, negative, general psychopathology as measured by PANSS, as well as side-effects as measured by AIMS, BAS, and SARS. The results were considered significant at 5% level.

8.2.4.8. Relationship between Cognitive and Symptomatic Improvement

Stepwise multiple linear regressions with the 6-week score as a dependent variable and the change scores (expressed as the percentage change from the baseline score) for the measures of symptomatology and side-effects as predictors were used to investigate the relationship between cognitive and symptomatic improvement. The baseline neuropsychological score (and atypical antipsychotic type where appropriate) was used as a covariate (i.e. entered the model as a forced entry). Predictors were considered to be significant at 5% level.

8.3. Results

8.3.1. Preliminary Data Screening

8.3.1.1. Data Distribution

The raw scores for WCST perseverative responses were positively skewed in both groups and were log transformed, which normalised the distribution at both time points.

8.3.1.2. Missing Data

There were a few missing values on some of the neuropsychological measures. One patient switched to olanzapine failed to complete CPT at the follow up. One patient switched to risperidone failed to complete CPT at the baseline, but found it possible to cope with the demanding nature of the task at 6 weeks. Both patients reported not being able to discriminate between the numbers despite making an attempt to do so.

The cases with the missing values were excluded from the analysis per variable.

8.3.2. Main Analyses

8.3.2.1. Test-retest Reliability of Neuropsychological Measures

All neuropsychological measures, excluding Hopkins Verbal Learning Task and Stroop interference, showed satisfactory test-retest reliability in the normal control group. Correlation coefficients ranged between .546 for Grooved Pegboard test and .876 for the Letter-Number test (all $p<.006$). Stroop interference scores of the baseline and 6 weeks performances showed a correlation of .398 ($p = .060$). However, after the exclusion of an obvious outlier as identified by using the scatterplot, the correlation improved to .475. HVLT scores correlated at .294, but after the exclusion of the outlier, the correlation improved to .552.

8.3.2.2. Normal Practice Effect

The normal practice effect on all measures was small and none was greater than 0.5 sd. The practice effect in normal controls reached statistical significance at 5% level on Logical Memory delayed recall ($z = .40$, $p = .023$), Trail B-A ($z = -.40$, $p = .027$), WCST perseverative responses ($z = -.44$, $p = .024$), CPT d'prime ($z = .42$, $p = .028$), and Stroop word reading ($z = .47$, $p = .007$). (See *Table 8.4.* for the baseline and 6 weeks raw mean scores mean, sd, change in z-scores, and p-values).

8.3.2.3. Effect of Atypical Antipsychotics on Neuropsychological Performance

Table 8.4 presents the descriptive statistics (raw score means, sd, and mean z-score change) for the patients' performance on conventional antipsychotics and after 6 weeks treatment with atypical antipsychotics. As can be seen from the table, the performance on four tests improved by more than .5 sd, including

HVLT, BSRT, GPB, and Letter-Number test, which is greater than the practice effect observed in normal controls on these measures.

TABLE 8.4. Change in neuropsychological performance from baseline to 6 weeks in patients treated with atypical antipsychotics and normal controls

		Mean (SD)			P value			
Neuropsychological Measure	**Group**	**Baseline**	**6 weeks**	**Mean z-score change**	**Within group**	**Time by atypical type**	**Time by group**	**Between group**
HVLT free recall	Patients	17.41 (5.75)	21.23 (4.58)	.77	.002$	.922	.067	.0002
	Controls	26.78 (4.94)	27.65 (4.70)	.18	.474	-		
BSRT total words recalled	Patients	45.74 (13.24)	57.14 (16.07)	.70	.001$	.080	.010	.0001
	Controls	69.39 (16.21)	68.22 (13.49)	-.01	.696	-		
Logical Memory immediate	Patients	8.55 (4.06)	9.00 (3.31)	.13	.346	.205	-	-
	Controls	12.17 (3.47)	12.45 (2.86)	.12	.477	-		
Logical Memory delayed	Patients	6.86 (3.99)	8.27 (2.80)	.46	.035	.618	-	-
	Controls	10.09 (3.06)	11.27 (3.04)	.40	.023	-		
BVRT number correct	Patients	4.91 (2.39)	4.23 (2.56)	.28	.177	.706	-	-
	Controls	6.52 (2.43)	6.76 (2.10)	.00	1.00	-		
Letter-Number total correct	Patients	8.09 (4.13)	13.50 (3.39)	1.57	.0004$	.419	.0003	.0002
	Controls	16.00 (3.44)	16.61 (3.37)	.18	.10	-		
Trail B-A*	Patients	55.52 (22.43)	61.18 (32.97)	.17	.337	.182	-	-
	Controls	44.26 (31.49)	31.65 (22.71)	-.40	.027	-		
WCST perseverative responses *	Patients	32.82 (32.42)	24.00 (15.42)	-.19	.353	.235	-	-
	Controls	15.09 (11.74)	9.50 (9.26)	-.44	.024	-		
CPT d'prime	Patients	.66 (.43)	.81 (.45)	.20	.124	.839	-	-
	Controls	1.49 (.96)	1.89 (1.17)	.42	.028	-		
Stroop interference score	Patients	1.30 (9.86)	-1.71 (5.03)	-.32	.213	.708	-	-
	Controls	3.28 (9.77)	1.63 (6.54)	-.17	.036	-		
Stroop word score	Patients	84.95 (14.92)	81.89 (19.46)	-.16	.403	.350	-	-
	Controls	100.52 (13.24)	106.70 (17.59)	.47	.007	-		
Stroop colour score	Patients	54.45 (9.18)	57.50 (15.03)	.25	.255	.332	-	-
	Controls	76.22 (17.05)	77.22 (13.63)	.00	.625	-		
Phonological Verbal Fluency	Patients	31.32 (10.06)	33.45 (9.41)	.16	.271	.230	-	-
	Controls	41.96 (13.24)	43.50 (13.12)	.13	.665	-		
Semantic Verbal Fluency	Patients	37.23 (10.69)	36.27 (6.57)	-.11	.591	.437	-	-
	Controls	48.57 (9.07)	47.14 (14.94)	-.17	.655	-		
Finger Tapping mean	Patients	40.21 (9.32)	41.14 (11.03)	.12	.622	.108	-	-
	Controls	46.77 (8.03)	48.28 (8.62)	.19	.306	-		
Grooved Pegboard mean*	Patients	117.27 (57.12)	95.32 (21.80)	-1.36	.023♦	.203	.013	.0006
	Controls	68.87 (16.09)	73.20 (16.48)	.27	.195	-		

* Higher score indicates poorer performance

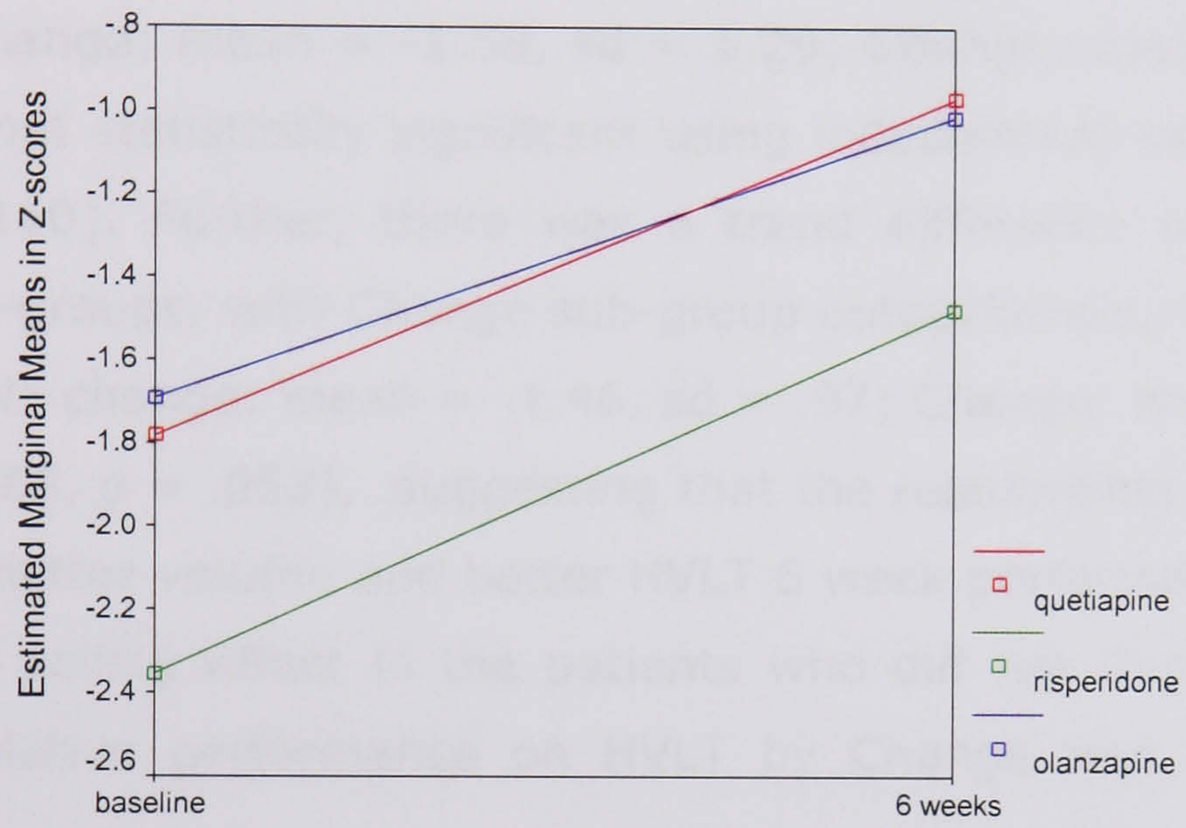
♦ Significant at 5 % level

$ Significant with Bonferroni correction (p = .003)

Hopkins Verbal Learning Test

The improvement of .77 sd was observed on HVLT total recall. The main effect of time of a mixed-model ANOVA was significant after Bonferroni correction [$F_{(1,19)}$ = 13.327, p = .002], with no significant time by atypical antipsychotic type medication interaction [p = .922], suggesting the patients improved regardless of which atypical antipsychotic they were switched to. (See *Figure 8.1.* illustrating the mean change in z-scores for patients treated with olanzapine, risperidone, or quetiapine).

FIGURE 8.1. Plot of HVLT performance change in mean z-scores from the baseline to 6 weeks for patients treated with olanzapine, risperidone, or quetiapine



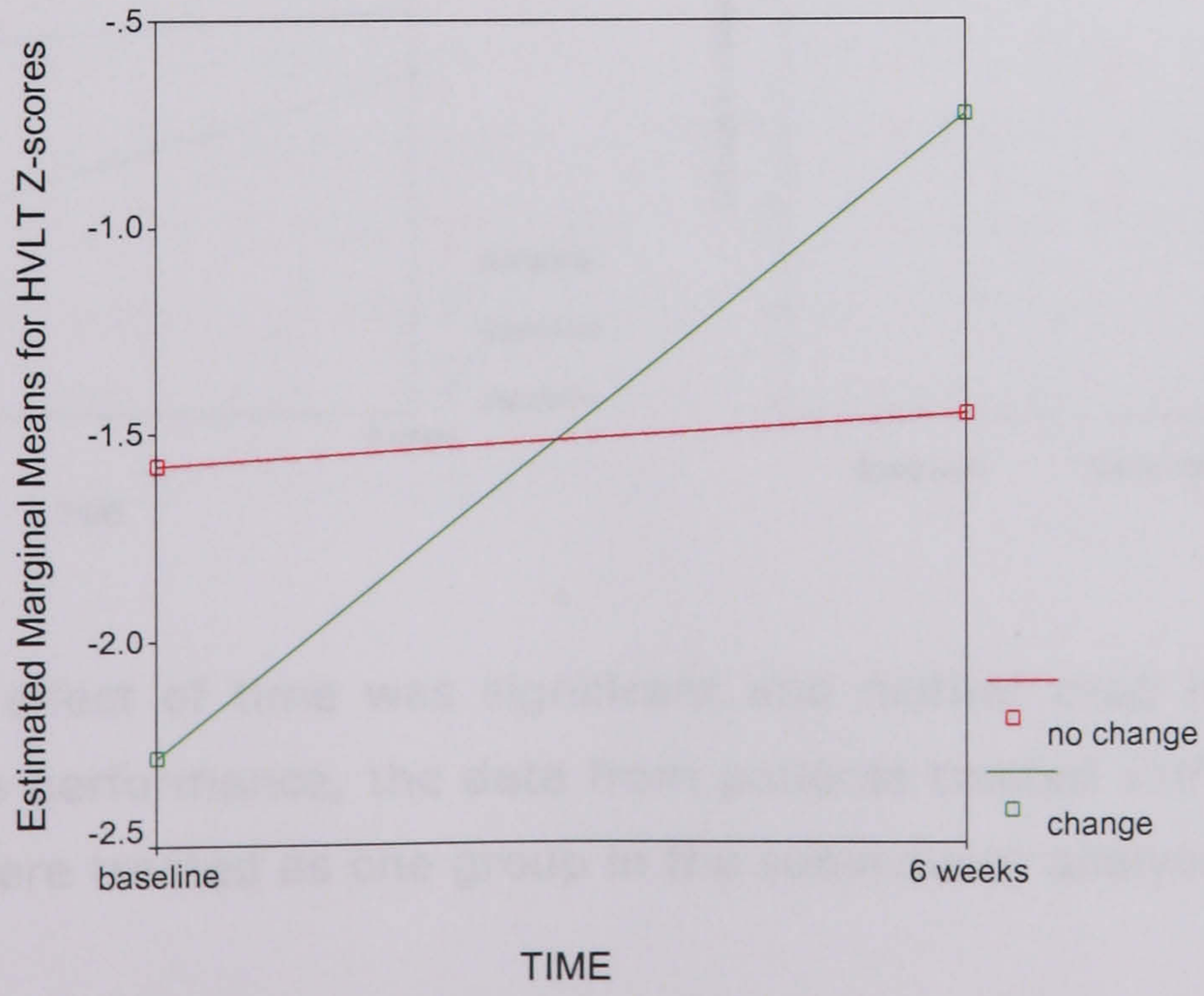
Patients improved in their HVLT performance more than would have been expected due to the normal practice effect, as evidenced by the trend for time by group interaction of a mixed-model ANOVA, with time as a within-subject factor, and group (patients vs controls) as a between-subject factor [$F_{(1,43)}$ = 3.539, p = .067]. There was also a significant between group main effect [$F_{(1,43)}$ = 38.621, p <.0001]. Post hoc between-group contrasts using independent samples t-tests with the Bonferroni correction (2 comparisons, p = .025) showed significant group differences at both baseline [$t_{(43)}$ = -5.874, p < .0001] and 6 weeks [$t_{(43)}$ = -4.645, p < .0001], suggesting that although the patients' performance has improved, it was significantly below the normal level. These differences remained after controlling for premorbid IQ [baseline: $F_{(1,42)}$ = 26.845, p = .0002; 6 weeks: $F_{(1,42)}$ = 12.720, p = .0005].

Stepwise multiple linear regression with HVLT 6 week score as the dependent variable, and with baseline HVLT z-score as a covariate (forced entry), showed that *smaller* grey matter volume of the precuneus was predictive of *higher* HVLT score at 6 weeks in patients [β = .-414; t=-2.600, r_p = -.512, p = .018],

accounting for 16% of the variance. The regression model including the baseline score and the precuneus grey matter volume accounted for 53% of the variance in 6 weeks scores [R^2 = .532, $F_{(1,19)}$ = 10.805, p = .001].

To ascertain that the relationship between smaller precuneus volume and greater HVLT performance improvement is not simply due to the ceiling effect, i.e. the fact that patients who did not show change in performance did not have a room for improvement due to scoring high at the baseline assessment, patient group was divided using the median split into two sub-groups: No change (n =12, mean change = .12, sd = .49) and Change (n = 10, mean change = 1.56, sd = .75). Change sub-group had lower mean HVLT baseline performance than No change sub-group (No change: mean = -1.58, sd = 1.29; Change: mean = -2.29, sd = .94), but it was not statistically significant using independent-sample t-test [$t_{(20)}$ = 1.461, p = .160]. Further, there was a trend difference in 6-week scores between two sub-groups, with Change sub-group outperforming the patients who did not change (No change: mean = -1.46, sd = .97; Change: mean = -.73, sd = .72; t(20) = -1.968, p = .063), suggesting that the relationship between smaller precuneus grey matter volume and better HVLT 6 week performance could not be explained by the ceiling effect in the patients who did not improve. *Figure 8.2* illustrates the relative performance on HVLT by Change and No change sub-groups.

FIGURE 8.2. The plot of HVLT performance in patients who showed and did not show improvement from the baseline to 6 weeks



Buschke Selective Reminding Test

An improvement of .70 sd was observed in patients after 6-week treatment with atypical antipsychotics on the BSRT total words recalled. A main effect of time of a mixed-model ANOVA was significant after the Bonferroni correction [$F_{(1,16)}$ = 14.659, p = .001], with a trend for time by group interaction [p = .080], suggesting differential effect of atypical antipsychotics on this measure. As can be seen from *Figures 8.3* illustrating mean change in z-scores for patients treated with three atypical antipsychotics, all sub-groups have shown positive change in scores, although olanzapine sub-group had very small increment in performance (Olanzapine: mean z-score change = -.19, sd =.73; Risperidone: mean z-score change = -.78, sd = .87; Quetiapine = -.81, sd = 1.35). As can be seen from the scatterplots of the change z-scores for individual cases (*Figure 8.4*), olanzapine sub-group was most heterogeneous in terms of performance change. Post hoc contrasts using a mixed-model ANOVA with the Bonferroni correction (3 comparisons, p=.016) revealed no significant time by atypical medication type interactions; however, there was a trend for a greater improvement with quetiapine than olanzapine [$F_{(1,11)}$ = 4.627, p = .055].

FIGURE 8.3. The plot of BSRT performance change in mean z-scores from the baseline to 6 weeks for patients treated with olanzapine, risperidone, or quetiapine

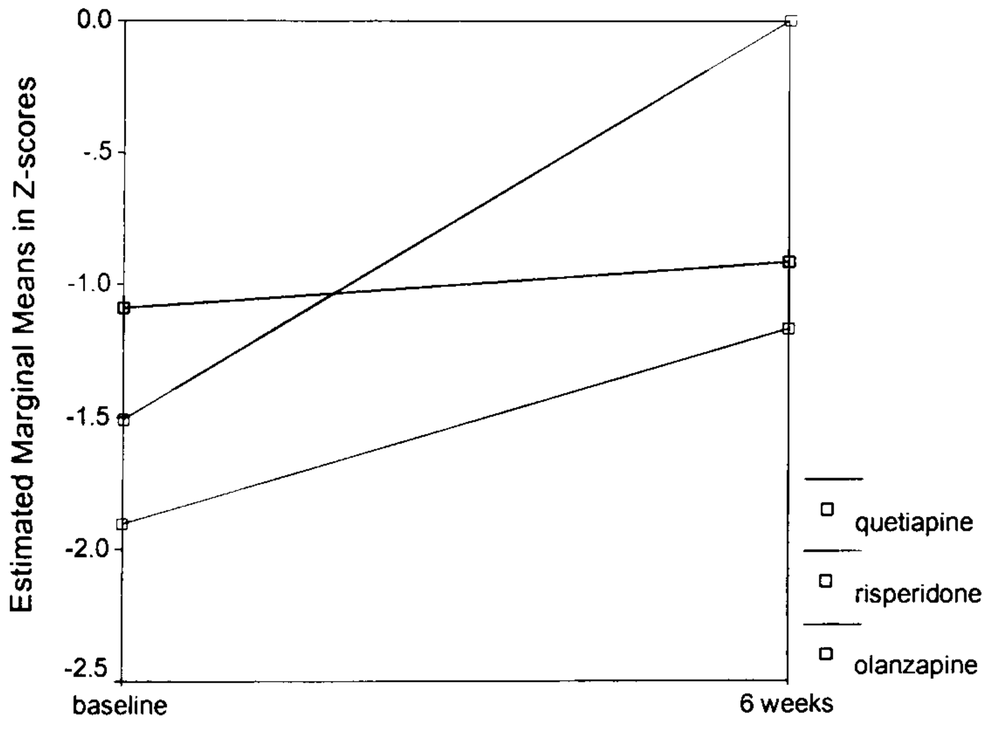
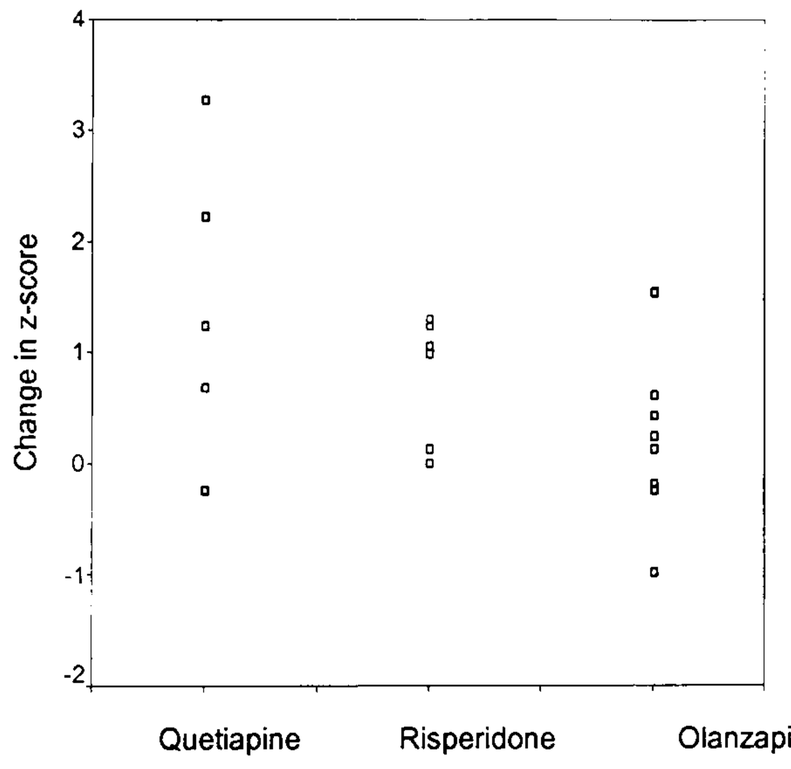


FIGURE 8.4. Scatterplot of change z-scores in GPB performance for patients treated with olanzapine, risperidone, or quetiapine



Since the main effect of time was significant and neither drug has produced a worsening of the performance, the data from patients treated with three atypical antipsychotics were treated as one group in the subsequent analyses.

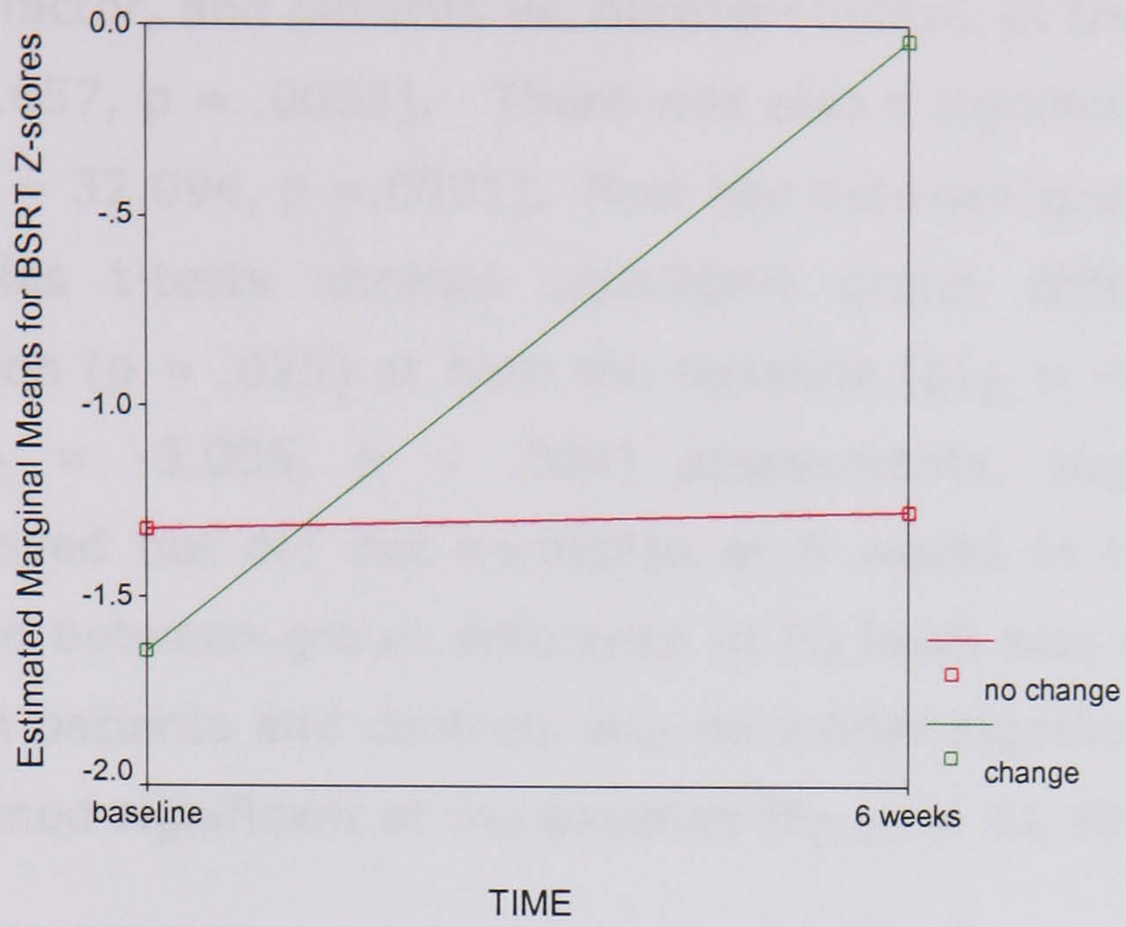
An improvement in patients after 6 weeks of atypical treatment in BSRT performance was significantly greater than what would be expected due to the normal practice effects, as evidenced by a significant time by group interaction of

a mixed-model Repeated Measures ANOVA, with the baseline and 6 weeks as the within-subject factor, and patients vs. normal controls as the between-subject factor [$F_{(1,40)}$ = 7.282, p = .010]. There was also a significant between group main effect [$F_{(1, 38)}$ = 18.583, p =.0001]. Post hoc between-group contrasts using independent samples t-tests showed significant group differences with the Bonferroni correction (p = .025) at both baseline [$t_{(40)}$ = -5.105, p = .0009] and 6 weeks [$t_{(40)}$ = -2.509, p = .016], suggesting that although patients' performance has improved, it was still below the normal level. However, after controlling for difference in premorbid IQ, the difference at 6 weeks was no longer significant using 1-way analysis of covariance (ANCOVA) [p= .089].

Stepwise multiple linear regression, with the baseline BSRT z-score and atypical antipsychotic type as forced entries, showed that *smaller* IFG grey matter volume was predictive of *higher* BSRT score at 6 weeks in patients [β = .-466; t=-2.792, r_p = -.585, p = .014], accounting for 21% of the variance in 6-week scores. The regression model including the baseline score, atypical antipsychotic type, and the IFG grey matter volume accounted for 51% of the variance in 6-week scores [R^2 = .506, $F_{(1,18)}$ = 3.799, p = .003].

To ascertain that the relationship between smaller IFG volume and greater BSRT performance improvement is not simply due to the ceiling effect, the patients were divided using the median split into two sub-groups: No change (n =11, mean change = .01, sd = .47) and Change (n = 8, mean change = 1.60, sd = .78). There was no significant difference in the baseline scores between Change (mean = -1.64, sd = .62) and No change (mean = -1.33, sd = .94) sub-groups using an independent-samples t-test [$F_{(1, 17)}$ = .831, p = .417], with a significant difference at 6 week (Change: mean = -.004, sd = 1.02; No change: mean = -1.27, sd = .71) [$t_{(17)}$ = -3.126, p =.006]. Therefore, the relationship between smaller IFG grey matter volume and greater BSRT improvement could not be explained by the ceiling effect. *Figure 8.5* illustrates the relative performance on BSRT by Change and No change sub-groups.

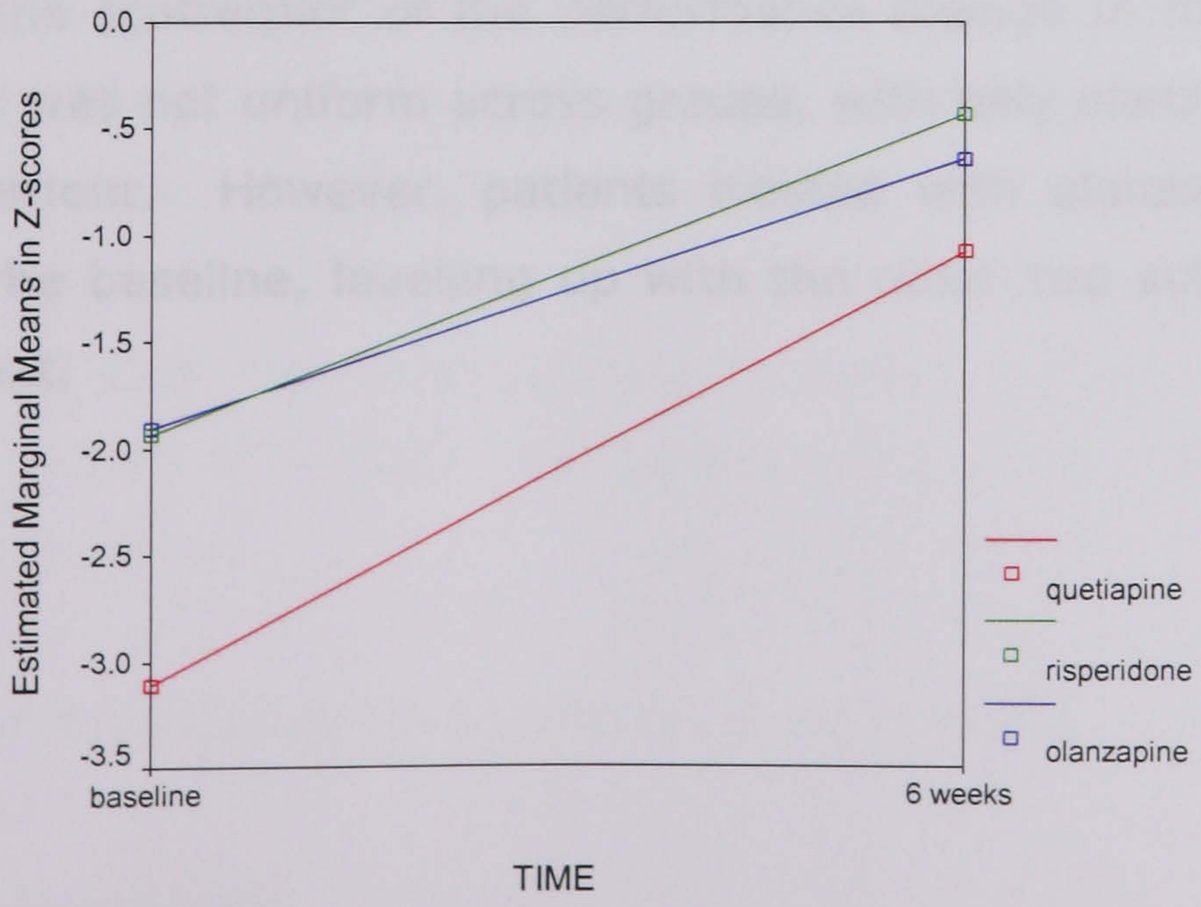
FIGURE 8.5. The plot of BSRT performance in patients who showed and did not show improvement from the baseline to 6 weeks



Letter-Number Test

An improvement of 1.57 sd was observed in patients after 6-week treatment with atypical antipsychotics on the measure of verbal working memory Letter-Number Test, which was significant after the Bonferroni correction [$F_{(1.19)}$ = 41.429, p = .0004]. The time by atypical antipsychotic type interaction was not significant (p = .419), indicating no differential effect of atypical antipsychotics on this cognitive function. (See *Figure 8.6* illustrating the mean change in z-scores for patients treated with olanzapine, risperidone, or quetiapine).

Figure 8.6. Plot of LNT performance change in mean z-scores from the baseline to 6 weeks in patients treated with olanzapine, risperidone, or quetiapine



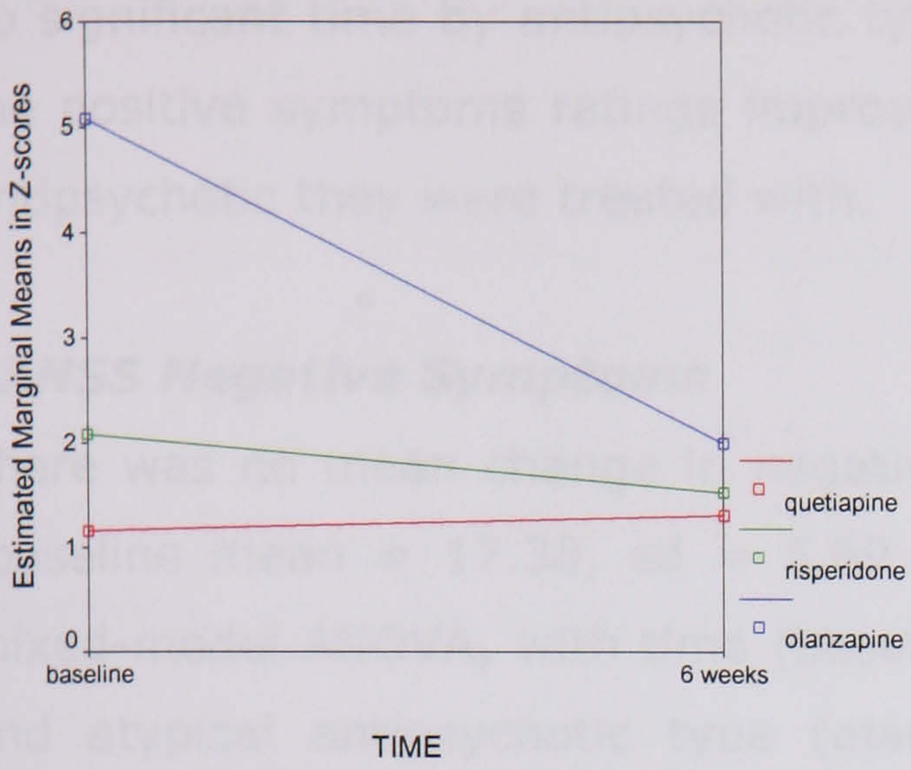
An improvement in patients was significantly greater than what would be expected due to the normal practice effect, as evidenced by the significant time by group interaction of a mixed-model ANOVA, with the baseline and 6 weeks as the within-subject factor, and patients vs. normal controls as the between-subject factor [$F_{(1,43)}$ = 28.657, p = .0003]. There was also a significant between-group main effect [$F_{(1, 43)}$ = 32.094, p =.0001]. Post hoc between-group contrasts using independent-samples t-tests showed significant group differences after the Bonferroni correction (p = .025) at both the baseline [$t_{(43)}$ = -6.997, p = .0007] and 6-week [$F_{(43)}$ = -3.085, p = .004] assessments, suggesting that the performance improved but did not normalise at 6 weeks in the patient group. However, when the between-group difference in IQ level was controlled for, the difference between patients and controls was no longer significant at 6 weeks [p = .117], but remained significant at the baseline [$F_{(1,42)}$ = 31.428, p = .0002].

No significant structural predictors of the 6-week LNT scores were found using stepwise multiple linear regression, with the baseline LNT scores as a covariate.

Grooved Peg Board

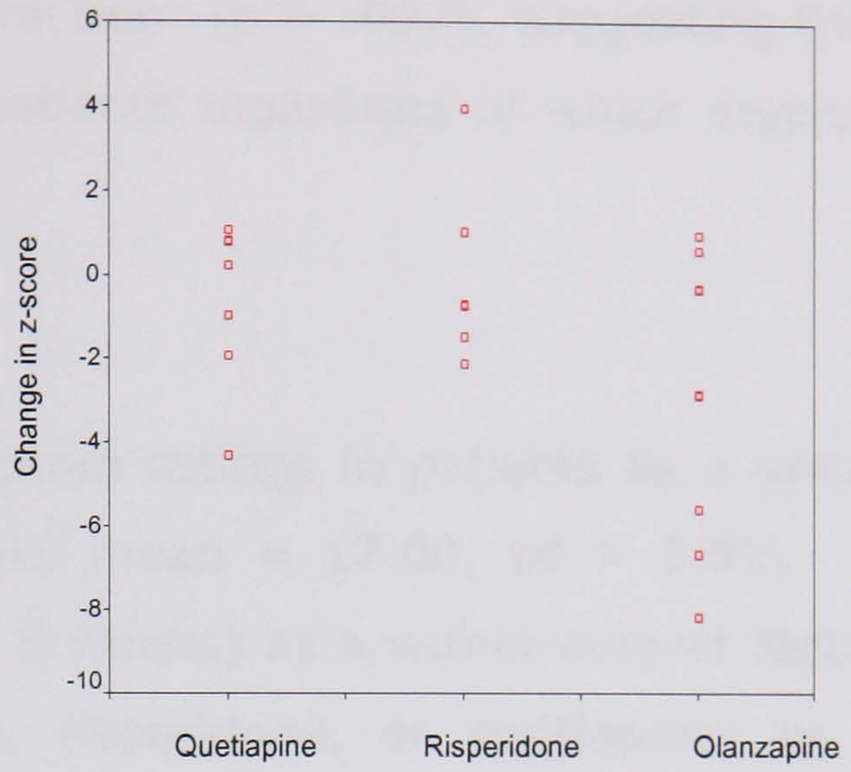
An improvement of 1.36 sd was observed in patients after 6-week treatment with atypical antipsychotics on the measure of dexterity, GPB. A mixed-model ANOVA with time (baseline vs. 6 weeks) and atypical antipsychotic type (olanzapine, risperidone, or quetiapine) showed a significant main effect of time at 5% level, but not significant with the Bonferroni correction [$F_{(1.19)}$ = 6.184, p = .023]. There was no significant time by atypical antipsychotic type interaction [$F_{(1.19)}$ = 1.744, p=.203], suggesting no differential effect of atypical antipsychotics with the present sample size. As can be seen from *Figures 8.7.* and *8.8.*, presenting the graph and the scatterplot of the performance change in three sub-groups, the improvement was not uniform across groups, with only olanzapine sub-group showing improvement. However, patients treated with olanzapine had worse performance at the baseline, levelling up with the other two sub-groups after 6 weeks of treatment.

FIGURE 8.7. The plot of GPB performance change in mean z-scores* from the baseline to 6 weeks for patients treated with olanzapine, risperidone, or quetiapine



* Lower mean indicates better performance

FIGURE 8.8. The scatterplot of z-scores change* in GPB performance for patients treated with olanzapine, risperidone, or quetiapine



* Lower change score indicates greater improvement

An improvement in patients was significantly greater than what would be expected due to the normal practice effect, since there was a significant time by group interaction of a mixed-model ANOVA, with time (baseline vs. 6 weeks) as the within-subject factor, and group (patients vs. normal controls) as the between-subject factor [$F_{(1,43)}$ = 6.776, p = .013]. There was also a significant between group main effect [$F_{(1,43)}$ = 18.353, p =.0001]. Post hoc between-group contrasts using independent-samples t-tests with the Bonferroni correction (p = .025) showed significant between-group differences at both baseline [$t_{(43)}$ = 3.907, p = .0003] and 6-week [$t_{(43)}$ = 3.851, p = .0004] assessments, suggesting that the performance improved but did not normalise at 6 weeks in the patient group. The between-group differences at the baseline and 6 weeks remained significant after controlling for the group differences in IQ [baseline: $F_{(1,42)}$ = 6.840, p = .012; 6 weeks: $F_{(1,42)}$ = 5.979; p = .019].

Stepwise multiple linear regression analysis revealed no significant structural brain volume predictors of 6 week GPB performance, after taking the baseline performance as a covariate.

8.3.2.4. Effect of Atypical Antipsychotics on Symptoms

PANSS Positive Symptoms

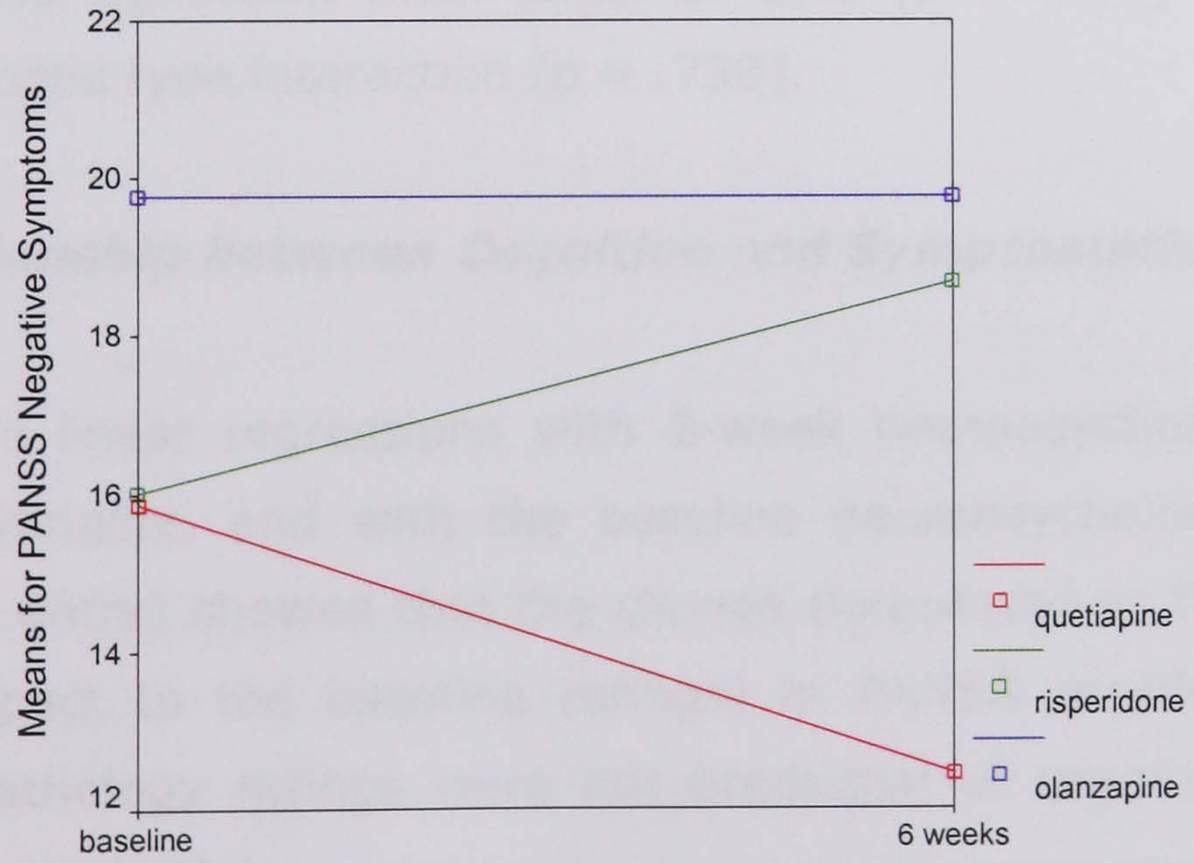
Positive symptom ratings decreased from the mean of 17.5 (sd = 6.94) to the mean of 13.47 (sd = 5.25) from the baseline to 6 weeks. A mixed-model ANOVA,

with time (baseline vs. 6 weeks) as a within-subject factor and atypical antipsychotic type (olanzapine, risperidone, or quetiapine) as a between-subject factor, revealed a significant main effect of time [$F_{(1,21)}$ = 5.673, p = .028], with no significant time by antipsychotic type interaction [p = .962], suggesting that the positive symptoms ratings improved in patients regardless of which atypical antipsychotic they were treated with.

PANSS Negative Symptoms

There was no mean change in negative symptom ratings in patients as a group (baseline mean = 17.38, sd = 5.69; 6 weeks mean = 17.00, sd = 5.95). A mixed-model ANOVA, with time (baseline vs. 6 weeks) as a within-subject factor and atypical antipsychotic type (olanzapine, risperidone, or quetiapine) as a between-subject factor, revealed no significant main effect of time [p = .794], with a trend for a time by antipsychotic type interaction [$F_{(1,21)}$ = 3.198; p = .065], suggesting a differential effect of atypical antipsychotics on negative symptoms. As can be seen from *Figure 8.9*, only patients treated with quetiapine showed a reduction in PANSS negative symptoms ratings. Risperidone sub-group appears to have worsened, whereas olanzapine group showed no change.

FIGURE 8.9. The plot of PANSS negative symptom ratings at baseline and 6 weeks for patients treated with olanzapine, risperidone, or quetiapine



PANSS General Psychopathology

There was a decrease in PANSS general psychopathology ratings in patients as a group from the baseline (Mean = 37.64, sd = 9.62) to 6 weeks (Mean = 33.05, sd = 7.61). A mixed-model ANOVA, with time (baseline vs. 6 weeks) as a within-subject factor and atypical antipsychotic type (olanzapine, risperidone, or

quetiapine) as a between-subject factor, revealed a trend for the main effect of time [$F_{(1,21)}$ = 3.868, p = .065], with no significant time by antipsychotic type interaction [p = .405], suggesting that the general psychopathology ratings improved in patients regardless of atypical antipsychotic type.

AIMS

There was a decrease in the ratings of abnormal involuntary movements as measured by AIMS from the mean of 2.33 (sd = 3.47) at the baseline to the mean of 1.14 (sd = 1.80) at 6-weeks assessment. However, the improvement was not statistically significant using a mixed-model ANOVA [p = .117], with no significant time by antipsychotic type interaction [p =.567].

Barnes Akathisia Rating Scale

There was a slight decrease in akathisia ratings as measured by BARS from the mean of 3.63 (sd = 3.25) to the mean of 2.63 (sd = 2.98). However, it was insignificant using a mixed-model ANOVA [p = .311], with no significant time by antipsychotic type interaction [p = .242].

Simpson Angus Rating Scale

There was no change in the ratings of parkinsonism as measured by SARS from the mean of 2.85 (sd = 2.25) to the mean of 2.89 (sd = 2.23). A mixed model ANOVA showed no significant main effect of time [p = .376] and no time by atypical antipsychotic type interaction [p = .730].

8.3.2.5. Relationship between Cognitive and Symptomatic Improvement

Stepwise multiple linear regressions with 6-week neuropsychological scores as the dependent variable, and with the baseline neuropsychological score as a covariate (forced entry) showed that the change (expressed as the percentage of change with respect to the baseline ratings) in PANSS positive symptoms or general psychopathology ratings were not predictive of cognitive improvement with atypical antipsychotics.

8.3.2.6. Relationship between Cognitive Improvement and Side-effects Change

Although there was no statistically significant improvement in motor, neurological, and autonomic symptoms, the change on AIMS, BAS and SARS was evaluated in relation to cognitive improvement to ascertain that cognitive

improvement was not simply due to the change in side-effects. Stepwise multiple linear regressions with 6-week neuropsychological scores as the dependent variable, and with the baseline neuropsychological score as a covariate (forced entry) showed that the change (expressed as the percentage of change with respect to the baseline ratings) in AIMS, BAS, or SARS ratings were not predictive of cognitive improvement with atypical antipsychotics.

8.3.2.7. Relationship Between Structural Alterations and Symptom Improvement

The predictive value of structural alterations was evaluated in relation to the improvement in positive and general psychopathology symptoms. Stepwise multiple regressions with 6 weeks symptoms scores as the dependent variable and global and regional structural volumes as predictors, with baseline symptoms scores as covariates showed that greater decrease in positive symptoms was associated with smaller precuneus [β = .570; t=3.066, r_p = .586, p = .007], accounting for 31% of the variance in 6-week scores. The regression model including the baseline score, and the precuneus volume accounted for 40% of the variance in 6-week scores [R^2 = .400, $F_{(2,18)}$ = 6.010, p = .010].

8.4. Discussion

The aim of the present study was to explore the validity of structural alterations as predictors of cognitive improvement with atypical antipsychotics. It was predicted that the patients would perform better on neuropsychological tests after being treated with atypical antipsychotics for a period of 6 weeks as compared with their performance on conventional antipsychotics. Greater cognitive improvement was hypothesised to be associated with less altered global and/or regional brain volumes.

The improvement was observed on four cognitive domains: immediate verbal memory (HVLT), verbal learning (BSRT), verbal working-memory (LNT), and dexterity (GPB). Verbal working memory improved by more than 1.5 sd in patients as a group, dexterity by 1.36 sd, whereas the improvement on immediate verbal memory and learning was more modest: .77 and .70 sd respectively, but all were significantly greater than practice effects observed in normal controls. The improved performance on LNT and BSRT approached normal

levels, after the differences in premorbid IQ between patients and controls were taken into account.

Greater improvement in immediate verbal memory was predicted by *smaller* volume of the precuneus. Although this finding is in accordance with the prediction that less altered structural volumes will be predictive of greater improvement, it is somewhat difficult to reconcile with the fact that larger precuneus was predictive of better verbal learning at baseline as found in Study 2 (*Chapter 7*). This relationship between HVLT performance change and precuneus volume could not be explained by the ceiling effect. The median split into sub-groups of patients who did and did not improve after 6 weeks of treatment showed that patients who improved had worse performance at the baseline, but outperformed the patients who did not change at the follow up, approaching normal control level (see *Figure 9.2*). These findings suggest that although patients with smaller precuneus perform worse than patients with larger precuneus whilst treated with conventional antipsychotics, they experience greater benefits from atypical antipsychotics for immediate memory function.

Interestingly, smaller precuneus was associated with greater reduction in positive symptoms. One of the findings of Study 1 (*Chapter 5*) was the association between larger precuneus and greater number of previous psychotic episodes. Therefore, it is possible that patients with larger precuneus might have treatment resistant positive symptoms that do not respond to either conventional or atypical antipsychotics. Somehow, however, larger precuneus in these patients allows them better episodic memory. Patients with smaller precuneus on the other hand, have benefited more from the atypical antipsychotic treatment, both in terms of psychotic symptom reduction and in terms of verbal memory improvement. Although psychotic symptoms and verbal memory dysfunction did not correlate, suggesting no causal relationships between them, they might be underlined by the same structural abnormality, namely precuneus enlargement, which, speculatively, results in greater vividness or salience of one's mental experiences, leading to better episodic memory, but predisposing to reality distortion in schizophrenia patients.

Greater improvement in verbal learning was predicted by *smaller* IFG volume. The direction of this relationship is contrary to the expectation, and could not be attributed to the ceiling effect. One possible interpretation of this finding is that patients with smaller IFG volume had greater severity of secondary negative symptoms induced by conventional antipsychotics, which were elevated when

they were switched to atypical antipsychotics, leading to better performance at the follow up. However, the results do not support this interpretation, since there was no association between IFG volume, negative symptoms ratings, and verbal learning performance either at the baseline or after the switch. Previous studies (Friedman et al., 1991; Molina et al., 2003a) reported positive associations between the measures of PFC integrity and volume and symptomatic improvement with clozapine. It is possible that the difference in the direction of associations between structural and functional variables in the previous and present studies is due to the difference in the assessed function, i.e. symptomatic vs. cognitive. The measure of the symptomatology, although susceptible to the investigator's bias, is exempt to practice effects. Cognitive performance, on the other hand, is a subject to many potential confounds, such as rapport with the experimenter, motivation, performance anxiety, understanding of the instructions, etc. It is possible to speculate that patients with larger IFG volume have performed to the best (or near the best) of their ability at the baseline, due to better executive functioning affording them greater 'adaptability' to the cognitive testing setting, and thus did not have much room for improvement at the follow-up. Patients with smaller IFG volume, on the other hand, might have had confounding factors affecting their performance at the baseline, such as difficulty in adjusting to the novel testing situation, understanding the instructions, etc. Against this suggestion, however, is the fact that IFG volume was not predictive of the improvement on other neuropsychological tests that would be dependent on its function, which would be subjects to similar influences. Pharmacologically, it is difficult to interpret why patients with smaller IFG volume would benefit from the atypical antipsychotic treatment, whereas patients with larger IFG volume would not. Studies are needed to replicate or refute the finding of the present investigation before an understanding can be reached. The improvement in verbal working memory (LNT) or dexterity (GPB) was not related to either global or regional structural brain volumes.

The improvement in all four cognitive domains was independent of the change in psychopathology as measured by PANSS or side effects as measured by AIMS, BAS, and SARS, suggesting a direct effect of atypical antipsychotics on cognitive deficits in schizophrenia.

Cognitive improvement with atypical antipsychotics in the present study was observed despite relatively low doses of haloperidol as a comparator. One of the ongoing controversies in relation to atypical antipsychotics superiority on cognition relative to typical antipsychotics is whether their effects can be

demonstrated relative to low doses of haloperidol. Traditionally high doses of haloperidol in clinical practice have little benefit or even a detrimental effect on cognitive function (Blyler and Gold, 2000). However, more recent studies investigating the effect of low doses of typical antipsychotics indicated that they might not have detrimental effects on cognition as traditional doses, with atypical antipsychotics showing no superiority over lower doses of typical antipsychotics (Green et al., 2002; Keefe et al., 2004). Therefore, cognitive superiority of atypical antipsychotics medication was called into question. Do atypical antipsychotics actually improve cognition or do they simply "afford a release from the deleterious effects, such as extrapyramidal symptoms (EPS), of inappropriately large doses of typical antipsychotics and concomitant adjunctive agents such as anticholinergics"? (Keefe et al., 2004; see also a debate on this issue between Meltzer & Sumiyoshi, 2003 and Carpenter & Gold, 2003). The results of the present study suggest that atypical antipsychotics effects on cognition could not be explained simply by the typical antipsychotic dose, since patients in the present study were on low doses of conventional medications, which were comparable to those used in Keefe et al. (2004) study. Neither they can be explained by the reduction in motor disorders associated with conventional antipsychotics, since, as discussed above, the motor side effect ratings were initially low and no further ascertainable change occurred. The discontinuation of anticholinergic medication might have played a role, since none of the patients required anticholinergic medication with atypical antipsychotics at 6 weeks. However, anticholinergic medication was only found to associate with LM performance in Study 2 (Chapter 6), but not with the tests that showed improvement in the present study. Cognitive efficacy of atypical antipsychotics is likely to be a combination of their pharmacological properties and release of typical medication deleterious effects.

It is interesting to note that the cognitive functions that have improved the most with atypical antipsychotic treatment included those that differentiated most reliably between schizophrenia patients and normal controls in Study 2 (Chapter 6), namely verbal working memory and learning. Both functions depend to some extent on the dorsolateral prefrontal cortex. Improvement in these functions might be due to the increased dopaminergic transmission in DLPFC attributable to serotonin-dopamine antagonism of atypical antipsychotics. Further, verbal working memory and learning are closely linked to the function of cholinergic system (Friedman et al., 1999). Conventional antipsychotics have consistently been shown to impair verbal learning due to the anticholinergic action and the need for anticholinergic medication to reduce EPS (Keefe et al., 1999). Previous

studies have found olanzapine, risperidone, and quetiapine to improve verbal working memory and learning, although the effect size for risperidone and quetiapine was found to be larger than that for olanzapine (Meltzer and McGurk, 1999). In the present investigation, patients treated with quetiapine and risperidone showed greater improvement in verbal learning than patients treated with olanzapine, with the difference between quetiapine and olanzapine sub-groups approaching significance. The absence of anticholinergic properties of risperidone and quetiapine might account for their greater efficacy on verbal learning than conventional antipsychotics or olanzapine. Due to its cholinergic properties, olanzapine did not produce as substantial increase in verbal working memory and learning as compared with conventional medication, but it did not have a detrimental effect either due to its dual serotonin-cholinergic antagonism (as discussed in *Chapter 3* of General Introduction, serotonin antagonism can alter anticholinergic effects). Thus, the limited sample of the present study provides further evidence that risperidone and quetiapine might have greater positive effect on verbal learning in schizophrenia than olanzapine. There was no evidence for the differential effect of three antipsychotics on other cognitive domains assessed in the present study. However, no firm conclusions can be drawn from the results of the present study in relation to the possible differential effect of three atypical antipsychotics on cognitive functioning in schizophrenia due to a very small sample size of the sub-groups.

The patients as a group showed improvement in positive symptoms and general psychopathology ratings, but not negative symptoms, as compared with haloperidol (the baseline). The results for negative symptoms indicated differential effect of three drugs, with quetiapine producing an improvement, olanzapine having no effect, and risperidone leading to worsening relative to the haloperidol baseline. Previous studies of risperidone did not observe such a detrimental effect of risperidone on negative symptoms, generally observing improvement in both positive and negative symptomatology compared to haloperidol (e.g. Gelders et al., 1990; Claus et al., 1992; Lindstrom et al., 1995; Jeste et al., 1997; meta-analysis: Glick et al., 2001). One recent study observed no improvement (Lindenmayer et al., 2004), whereas the result of another study (Marder and Meibach, 1994) suggested that negative symptom improvement might be specific to 6mg and 16mg of risperidone. The dose of risperidone in the present study was 2 mg, which was not found to be more effective for negative symptoms than treatment with haloperidol (Marder and Meibach, 1994). In a recent review of clinical efficacy of atypical antipsychotics in schizophrenia, risperidone, olanzapine, and quetiapine were found to have equal effect on

positive and negative symptomatology (Serretti et al., 2004). Therefore, the results of the present study suggesting differential effect of three atypical antipsychotics on negative symptoms might be due to the low dose of risperidone as well as small sample size producing spurious findings. In addition, patients in olanzapine sub-group had greater severity of negative symptoms (average score of around 20 points as compared with 16 points for quetiapine and risperidone), which might have biased the assessment of the effect of olanzapine on negative symptoms unfavourably.

The findings in relation to test-retest reliability of the neuropsychological measures in normal controls indicate that HVLT and Stroop interference might not have as high reliability as would be desirable for repeated testing. This finding casts doubts on the observed improvement on HVLT performance in schizophrenia patients, which might be a result of low reliability of this measure. It should be noted, however, that the improvement was observed in patients treated with three different antipsychotics to the same extent, indicating a systematic effect, rather than a spurious one.

More generally, the estimation of practice effect for the neuropsychological measures from healthy controls may not be adequate for the evaluation of the cognitive efficacy of atypical antipsychotics due to the fact that practice effects in schizophrenia are poorly understood (Beglinger et al., 2003). Therefore, to exclude the possibility that the improvement on neuropsychological measures observed in the present study is not simply due to low performance stability in patients, a control group of patients on conventional medications would have been desirable in the present study. This would have allowed estimating practice effects in schizophrenia patients (albeit confounded by the use of conventional medication). However, there were practical limitations preculiding the use of such patient control group, due to difficulty in recruiting patients that are maintained on conventional antipsychotics. It should be noted, however, that a none of the tests in the present study showed negative change, and that other tests on which performance have improved in patients showed high test-retest reliability and small practice effect in normal controls. Therefore, the results of the present study are unlikely to be fully explained by such possible confounds.

To conclude, the strengths of the present study were (i) within-subject design; ii) (ii) normal control group allowing for estimation of test-retest reliability practice effects; and (iii) low doses of conventional antipsychotics as a comparator. Improvement with atypical antipsychotics was found on the tests of verbal

memory and learning, verbal working memory, and dexterity. Contrary to the expectation, cognitive improvement on verbal immediate memory and verbal learning was predicted by *smaller* structural volumes of the precuneus and the IFG respectively. Improvement in verbal working memory and dexterity was not predicted by either global or regional structural volumes or change in psychopathology and/or side effects.

PART III

CHAPTER 9: GENERAL DISCUSSION

CHAPTER 9. GENERAL DISCUSSION

9.1. Chapter Overview

This chapter summarises and integrates the findings of the empirical investigations described in this thesis and attempts to place them in the context of the previous research. First, the aims and the theoretical underpinnings are reviewed, followed by the summary of the key findings. Further, the implications of the key findings for the schizophrenia research are outlined. Finally, methodological considerations and suggestions for future research are made.

9.2. The Overview of the Aims and Hypotheses

The main theoretical underpinning of the present investigation is that structural volume abnormalities characteristic of schizophrenia underlie its functional dysfunction, manifesting, amongst other things, as cognitive deficits, which can be quantified by the standard neuropsychological tests. These cognitive deficits are known to affect social, occupational, and personal success of individuals with schizophrenia and, therefore, became one of the treatment targets. Atypical antipsychotics are thought to have ameliorating effect on cognitive deficits as compared to conventional or typical antipsychotics. Therefore, the general aims of the present investigation were:

1) to quantify structural volume alterations in schizophrenia using a state-of-the-art automatic method of voxel-based morphometry, which surpasses the limitations of the traditional manual region of interest approach (see section 2.2.1);
2) to investigate the relationship of these structural volume alterations to the cognitive deficits as quantified by standard neuropsychological tests;

3) to explore the value of the structural volume alterations in predicting treatment response to atypical antipsychotics in terms of cognitive improvement.

To these aims, four experimental studies were conducted. The research problem, the aim, and the hypotheses of each study are summarised next.

9.2.1. Study 1: Structural Alterations in Schizophrenia: A Voxel-Based Morphometry Study

The aim of the first study was to identify the pattern of structural alterations in schizophrenia patients using the VBM technique. Currently, there are two main pre-processing protocols used for VBM: 'standard' and 'optimised'. The optimised protocol involves many more steps compared to the standard protocol, one of which is the construction of the study specific (i.e. based on the study's sample) template for the normalisation and segmentation of the brain images. Although theoretically optimised protocol should yield superior segmentation of the brain into its constituting tissue types, i.e. grey, white, and CSF, it has not been tested directly in a clinical population as to whether optimised protocol presents an advantage over more concise and hence less time consuming standard protocol. Therefore, the aims of Study 1 were twofold:

1) To identify a pattern of structural alterations in schizophrenia population using VBM method;
2) To compare standard and optimised VBM protocols in schizophrenia population in terms of tissue segmentation accuracy.

It was hypothesised that:

1) Patients with schizophrenia would have global and regional structural volume alterations. Apart from the regional alterations extensively studied with the ROI approach, such as STG, hippocampus, and basal ganglia (reviewed in Chapter 2), patients were hypothesised to have alterations of IFG grey matter volume, which have been relatively consistently identified in previous VBM studies, as well as brain regions thus far neglected by ROI studies, such as parietal and occipital cortex. No reduction of white matter volume was predicted since it is not found as consistently as that of the grey matter.

2) Optimised protocol would result in superior tissue segmentation compared with standard protocol.

A secondary aim of the study was to investigate the inter-relationships between structural volume alterations in schizophrenia and compare them with controls. This research question was motivated by the suggestions of the previous research that normal volumetric associations between different regions and structures of the brain might be altered in schizophrenia. Based on the previous research, it was hypothesised that schizophrenia patients will present with fronto-temporal dissociation, such that frontal and temporal volumes will be positively correlated in normal controls but not in patients.

9.2.2. Study 2: Cognitive Deficits in Schizophrenia

The primary aim of the second study was to ascertain the presence of cognitive deficits in the cohort of patients recruited for the present investigation. To this end, a neuropsychological battery was designed. All tests selected are standardised neuropsychological measures that have been consistently applied to assess neuropsychological deficits in schizophrenia population. The choice of the tasks has been motivated by the need to cover those cognitive domains that:

(i) have been shown to be central to the cognitive impairment in schizophrenia;

(ii) have a direct link with function outcome;

(iii) have been found to correlate with structural measures in the ROI studies;

(iv) are known to be unaffected or worsened by conventional antipsychotics; and are likely to be sensitive to pharmacological changes induced by atypical antipsychotics;

The battery taps into neurocognitive processes of verbal working memory, executive function, immediate and delayed memory and learning, immediate visuo-spatial memory, verbal fluency, sustained and selective attention, speed of information processing, and fine motor function.

It was hypothesised that patients will have deficits on all cognitive domains, with the most severe impairment on the tests of verbal memory and learning, as has been found by the previous research (see Chapter 2). Further, cognitive deficits were expected to be independent of symptomatology.

9.2.3. Study 3: Relationships between Structural Alterations and Cognitive Deficits

Chapter 2 reviewed comprehensively ROI studies investigating the relationship between structural and cognitive variables in schizophrenia. As has been discussed in the chapter, most ROI studies noted discrepancies in the structure/neurocognition relationships between patients and controls. The differences in structure/neurocognition correlations between the groups were of two sorts: i) those specific to schizophrenia patients (i.e. not seen in controls), and ii) those lacking in patients (i.e. significant in controls, but are not observed in patients). It is not clear, however, whether these differences pertain to statistical artefacts (i.e., different ranges of structural volumes and neuropsychological performance resulting in different correlation strength) or whether they reflect altered structure/neurocognition relationship in schizophrenia. Furthermore, only one study (Flaum et al., 1996) has formally tested the differences in the correlations between patients and controls statistically. Therefore, it is not currently clear whether the observed discrepancies significantly differentiate patients and controls. Finally, previous studies have not made an explicit distinction between the investigations of structural alterations/neurocognitive deficits relationships vs. structure/neurocognition relationships.

Study 3 was conducted to clarify these issues. It has utilised the VBM method for its power to identify localised tissue availability alterations throughout the entire brain with the aim to investigate whether: i) structural volume alterations are associated with cognitive deficits that are most characteristic of schizophrenia patients and ii) the structure/neurocognition relationship in schizophrenia is significantly altered in relation to healthy individuals. Note that the aim of the study was to investigate specifically the role of structural alterations (not structural volumes *per se*) in cognitive deficits in schizophrenia.

It was hypothesised that: (i) structural volume alterations identified in study 1 would be associated with cognitive deficits identified in study 2; (ii) there would be structure/cognitive relationships specific to schizophrenia; and (iii) there would be structure/cognitive relationships lacking in patients. More specific hypotheses as to the relationship between structural volumes and cognitive deficits were made in the Method section of Study 3 where previous findings on structural alterations/cognitive deficits were summarised.

9.2.4. Study 4: Structural Alterations as Predictors of Treatment Response to Atypical Antipsychotics

The first line of treatment for schizophrenia is pharmacological intervention with antipsychotic medication. New generation of antipsychotic drugs have greater efficacy in treating cognitive deficits, which, as discussed in *Chapter 3*, are better predictors of functional outcome, than conventional drugs.

Three most commonly applied drugs in clinical practice, risperidone, qutaipine, and olanzapine, share the main pharmacological property, namely dopamine-serotonin antagonism, which seems to underlie their greater cognitive efficacy. The aim of this study was to investigate the validity of structural brain alterations (identified in Study 1) in predicting cognitive improvement after 6 weeks of treatment.

It was hypothesised that greater severity of structural alterations, both global and local, would be predictive of poorer response to atypical antipsychotics in terms of cognitive improvement following 6 weeks of treatment.

9.3. Summary of the Key Findings

The key findings of the investigations conducted to assess the above hypotheses are as follows. First, optimised VBM protocol had superior registration to the standard one and revealed both global and regional reductions of grey and white matter in schizophrenia patients. Regional alterations were specific to the left hemisphere and included significant reduction of the IFG and STG grey matter volume, a trend for white matter volume reduction of parietal and occipital lobes, and a trend for grey matter volume increase in the putamen and the precuneus. Contrary to the prediction and the findings of previous studies, the patients did not show fronto-temporal dissociation. Second, patients displayed cognitive deficits on all domains assessed, with the particular impairment on the tests requiring verbal function, including verbal learning and memory, verbal working memory, and verbal fluency. Deficits of working memory and learning, and speed of information processing differentiated patients and controls most reliably. Third, there were a number of associations between structural volume alterations and cognitive deficits in patients, some of which were specific to patients. Patients also lacked a number of association observed in controls. Specifically,

smaller global brain volume was associated with poorer phonological verbal fluency; smaller grey matter volume was associated with lower premorbid IQ and poorer dexterity, with the later association being specific to patients. Enlarged precuneus was associated with *better* verbal learning in patients, with this relationship being specific to schizophrenia. The function of verbal learning as well as verbal and non-verbal memory was associated with the volume of IFG significantly stronger in controls than in patients. This dissociation between two groups in terms of the regional structural volume/memory and learning relationship was perhaps the most striking finding. Larger volume of the precuneus was associated with poorer verbal working memory in controls, significantly differentiating them from patients. The deficits in the speed of word reading and colour naming in patients were associated with the reduced white matter volume of the occipital lobe, whereas these structure/cognition relationships were not observed in controls. Fourth, patients showed improvement in verbal memory and learning, verbal working memory, and dexterity after 6-week treatment with atypical antipsychotics. However, contrary to the prediction, cognitive improvement was not associated with larger brain volumes. Instead, smaller IFG volume was found to be predictive of greater improvement in verbal learning, whereas smaller precuneus was found to be predictive of greater improvement in immediate verbal memory.

9.4. Implication of the Key Findings for Schizophrenia Research

9.4.1. Structural Alterations

The present thesis adds to the weight of the evidence for the existence of structural volume alterations in individuals diagnosed with schizophrenia (e.g. Shenton et al., 2001, *Chapter 2*). Characteristically, regional alterations in the present cohort were restricted to the left hemisphere. There was a cluster of grey matter volume reduction observed in the right IFG, but it was not significant with the statistical criteria for the VBM method adopted in the present study and elsewhere (e.g. Wright et al., 1995; Wilke et al., 2000; Ananth et al., 2002). The observed left hemisphere alterations were present in patients as a group regardless of their age, gender, or global tissue volumes. The pattern of the alterations of the grey matter volume was widespread, affecting primarily cortical heteromodal association areas, such as IFG, anterior STG, and the precuneus, but also primary sensory area of the visual cortex, and sub-cortically putamen.

Patients with family history of schizophrenia were found to have smaller STG volume than patients with no family history. It is possible that in patients with genetic loading STG volume reduction might represent a neurodevelopmental anomaly with possible further degeneration following the illness onset. The possible difference in STG volume in familial and non-familial schizophrenia should be investigated further.

Compared with other VBM studies, the patients of the present cohort had relatively few structural alterations relative to normal controls, restricted to the left hemisphere. Most VBM studies observed bilateral alterations of tissue density and volume (e.g. Wright et al., 1999; Wilke et al., 2001; Ananth et al., 2002; Job et al., 2002). One study (Suzuki et al., 2002) observed predominantly left hemisphere grey matter density reductions in schizophrenia males, including that of medial frontal and superior temporal gyri, but right hemisphere grey matter density reduction in schizophrenia females, including that of superior and medial frontal gyrus. It is possible that right IFG reduction in the present cohort was mediated by gender, and therefore did not attain significance, since the gender was controlled for in the analysis. Although bilateral reductions were noted in the majority of the studies, left hemisphere tended to be affected more severely, with more altered regions and with the alterations having greater spatial extent (i.e. greater number of voxels in the cluster of altered brain tissue) than those observed in the right hemisphere. Many ROI studies of schizophrenia patients have also noted predominantly left hemisphere abnormalities in right-handed subjects, particularly in the lateral and medial temporal lobe structures (e.g. Barta et al., 1990; Bogerts et al., 1990; Shenton et al., 1992; Wible et al., 1995; Velakoulis et al., 1999; Kwon et al., 1999). The right hemisphere, especially the temporal area, develops earlier than the left for a short period of time, which may result in it being less likely to be impaired (Gerschwind and Galaburda, 1985). Therefore, the period of vulnerability is more prolonged on the left, which could make it more prone to injuries. It is, however, unknown whether disturbances in the left hemisphere are related to genetic or environmental factors. The study by Reveley and colleagues (1987) of eleven monozygotic twin pairs discordant for schizophrenia and 18 control monozygotic twin pairs using CT revealed that the left hemisphere was less dense than the right in twins with schizophrenia, while the reverse was found for the co-twins and controls. These results suggest that left hemisphere abnormality is environmentally acquired, rather than a genetic trait. In any case, if there were an insult to the fetal brain in the process of neurodevelopment, environmental or otherwise, the left hemisphere would be more prone to disruption, which could possibly be related to

the pathogenesis of schizophrenia. It should be born in mind, however, that many of the key areas implicated in schizophrenia, including sub-regions of the PFC, lateral and medial temporal lobe structures, basal ganglia, sub-regions of the parietal lobe and others were found to be affected bilaterally in some studies (e.g. Baare et al., 1998; Wright et al., 1999; Cannon et al., 2002).

The most pronounced reduction of the grey matter volume in the present cohort was observed in the IFG and anterior STG. The volume reduction of these areas was also correlated in patients. As has been discussed in *Chapter 5*, these areas are related structurally and functionally, representing a part of a neuronal circuit associated with semantic processing and memory (e.g. Binder et al., 1997; Rao et al., 1997; Mummery et al., 1999). The studies of language disturbance in schizophrenia patients showed that semantic domain is more prominently deviant than phonological or syntactic (review, DeLisi, 2001). Study 2 (*Chapter 6*) found the most severe performance deficits in schizophrenia patients on the tests requiring semantic processing, comprehension, and production. As other studies, the present investigation observed greater deficits in semantic than phonological verbal fluency. Further, patients with familial history of schizophrenia had significantly greater reduction of the anterior STG than patients without family incidences. Previous studies (e.g. Condray et al., 1992; Goldberg et al., 1995; Niendam et al., 2003) showed that disturbances in semantic system are also apparent in unaffected relatives of schizophrenia probands. Moreover, as discussed before (Study 1, *Chapter 5*), the reduction of the anterior STG volume distinguishes patients with schizophrenia from those with bipolar disorder (Pearlson, 1997). Taken together, these findings suggest that abnormal structure and function of the semantic system might represent an endophenotype and a risk factor for schizophrenia.

As discussed in *Chapter 5*, previous studies investigating the inter-relationships between the volumes of different brain structures in schizophrenia reported conflicting results as to the relationship between PFC and STG. Specifically, whereas Wible et al. (1995) observed significant positive correlations between the volumes of left PFC grey matter and anterior STG (as well as anterior medial temporal lobe structures) in schizophrenia patients but not in normal controls, Woodruff et al. (1997b) reported a dissociation between the total volumes of PFC and STG in patients with the relationship being significant in normal controls. The present investigation (Study 1, *Chapter 5*) has found the grey matter volumes of IFG and anterior STG to correlate to a similar extent in both patient and control groups. The differences in measurements, such as total versus grey matter

volume, or anterior/posterior STG versus total STG volume, might contribute to the differences in the findings between the studies. Due to the substantive structural and functional connections between PFC and STG, it is likely that the development of these brain regions is temporary related. Inter-relationship between different brain regions is poorly understood in healthy as well as abnormal development. Establishing whether there is dissociation or increased association between the volumes of these brain regions in schizophrenia patients relative to healthy individuals might be important for understanding the pathogenesis of schizophrenia. For example, the primary abnormality in the anterior STG due to genetic factors, as suggested by the greater reduction of this region in patients with family history of schizophrenia, might result in abnormal development of the PFC regions structurally and functionally related with the STG by the virtue of disrupted mutual trophic influence on establishing axonal connections (Caviness and Takahashi, 1995) and/or programmed synaptic pruning (Keshavan et al., 1994). Grey matter losses throughout childhood and adolescence are concentrated in the frontal and parietal but not in the temporal and occipital cortical areas in normal brain development (Rapoport et al., 1999). Therefore, reductions in the IFG volume might be due to the failure to establish distant synaptic connections, leading to overpruning of synapses, and thus reduced volume.

The present investigation did not observe alterations in the volume of the medial temporal lobe structures in schizophrenia patients. The abnormality of the hippocampal complex in particular is a central feature of many accounts of schizophrenia pathogenesis and pathophysiology (e.g. Torrey and Peterson, 1974; Conrad and Scheibel, 1987; Weinberger and Lipska, 1995; Gothelf et al., 2000). Data from schizophrenia patients (Gothelf et al., 2000) suggest that developmental abnormalities of the hippocampus may be aetiological. In addition, excitotoxic lesion of the ventral hippocampus in rodents and primates leads to behavioural and neurophysiologic defects similar to those seen in affected humans (Lipska et al., 1995; Bachevalier et al., 1999). The studies of monozygotic twins discordant for schizophrenia consistently demonstrate smaller hippocampal volume in the affected twin (Suddath et al. 1990; McNeil et al. 2000; Baare et al., 2001), with this difference most likely being due to non-genetic factors such as obstetric complications (McNeil et al., 2000). Supporting this argument, Stefanis et al. (1999) reported hippocampal volume reductions in patients with no familial history of schizophrenia but with the history of obstetric complications relative to the patients with familial history of schizophrenia but without the history of obstetric complications and normal controls. In a more

recent study from the same laboratory Schulze and co-workers (2003) showed that the association between obstetric complications and hippocampal volume is not confined to patients with no familial history, but is also observed in patients with familial history. Therefore, the inconsistency of the evidence for the hippocampal involvement across neuroimaging (reviews, Nelson et al., 1998; Shenton et al., 2001) and post-mortem studies (review Dwork, 1997) might be due to the inclusions of the subjects with and without the history of obstetric complications. In the present investigation, obstetric history of the participants was not available. If the majority of the patients in the present cohort did not have obstetric complications or, alternatively, there was a similar number of patients and normal controls exposed to obstetric complications, these sample compositions might explain the negative finding in relation to the hippocampus. Future studies of schizophrenia pathophysiology need to include the history of obstetric complications as a confounding variable to control for its putative relationship with hippocampal volume. In addition, as discussed in *Chapter 5*, the VBM technique might not be sensitive enough to identife hippocampal changes due to the difficulty in differentiating grey and white matter in these areas (Velakoulis et al., 1999; Ashburner and Friston, 2000). However, some of the previous VBM studies have implicated medial temporal structures in schizophrenia patients using similar methodology (e.g. Wright et al., 1999; Job et al., 2002; Kubicki et al., 2002; Suzuki et al., 2002).

The findings of the present thesis do not provide support for the structural volume pathology of either thalamus or cerebellum in schizophrenia. Andreasen et al. (1996; 1998; 1999) proposed that schizophrenia might be characterised by abnormal connectivity between prefrontal cortex, thalamic nuclei, and the cerebellum. This abnormal cortico-cerebellar-thalamo-cortical circuitry (CCTCC) will functionally manifest as cognitive dysmetria, i.e. disruption in processing, prioritising, retrieval, coordination, and responding to information. An attractive feature of the model proposed by Andreasen is that cognitive dysmetria, as a disorder of the CCTCC, may provide a heuristic theoretical framework for strategies to explore aetiology, pathophysiology, intervention, and prevention of schizophrenia. One of the long-lasting controversies about schizophrenia, as discussed in Chapter 1, is whether there is a unifying phenotype underlying the condition or whether it is a heterogeneous disorder. Cognitive dysmetria model offers a unifying framework, defining schizophrenia phenotype by a specific abnormality of a functional neuronal circuit, which can potentially produce a diversity of symptoms characteristic of schizophrenia. There is some support for the model from the functional imaging studies using both PET (e.g. Andreasen et

al., 1996; Wiser et al., 1998; Crespo-Facarro et al., 1999) and fMRI (e.g. Schlosser et al., 2003) that demonstrated disrupted function of CCTCC in schizophrenia patients during rest and cognitive activation paradigms. Morphometric MRI studies from Andreasen's laboratory have reported abnormal volumes of the thalamus (Andreasen et al., 1994) and the cerebellar vermis (Nopolous et al., 1999) in schizophrenia patients. Investigators from an independent laboratory (Volz et al., 2000) have confirmed thalamic and cerebellar abnormalities in the same sample of patients using deformation-based morphometry. However, only one study using VBM (Ananth et al., 2002) observed thalamic reduction in schizophrenia and two studies reported grey matter increases in the cerebellum (Wilke et al., 2001; Suzuki et al., 2002), which might be more prominent in affected women (Suzuki et al., 2002). The present investigation adds to the negative findings in relation to thalamic and cerebellar structural pathology in schizophrenia. However, it should be noted that the measurement of thalamic nuclei using either ROI or VBM approaches is complicated by the fact that the grey/white matter segmentation is problematic in this region due to the blurred boundaries between two tissue types. Magnotta and co-workers (2000) developed new MR pulse sequence, cortex attenuated inversion recovery, which increases the contrast-to-noise in MRI scans allowing the imaging of the individual thalamic sub-nuclei. Perhaps future studies using this acquisition sequence will either confirm or refute the presence of thalamic reduction in schizophrenia. In addition, thalamic reduction might be confined to the patients with earlier onset, as found by two studies (Corey-Bloom et al., 1995; Jeste et al., 1998). Since patients of the present cohort had the average age of onset in early adulthood, they might not present with significantly smaller than normal thalami.

Finally, the important contribution of the present thesis to the field of schizophrenia research is the demonstration that the standard VBM protocol using MNI template may not be adequate for the pre-processing of the structural images of individuals with schizophrenia. The present investigation could not determine, considering the time constraints, weather the misregistration was the result of the use of the MNI template or the standard protocol or the combination of both. The misregistration had most likely occurred due to the enlarged ventricles of schizophrenia patients, which led to the distortion of the grey matter surrounding them during the spatial normalisation. Optimised protocol with customised template has rectified the problem. Future research may want to systematically vary the parameters of the pre-processing steps to determine the influence of different factors on the pre-processing accuracy. This question is of

great practical importance, since the standard protocol is much less time and computer consuming. If it were to be shown that customised template including the sca sans from patients is the deciding factor, the application of the standard protocol might be the desired option for the researchers. In addition, Wilke et al. (2003) have shown that less manipulation of the images leads to better detection of the cortical grey matter malformations in the temporal lobe epilepsy. It is not known whether the same applies to the detection of structural alterations in patients with schizophrenia.

In summary, the findings of the present investigation on structural brain alterations in schizophrenia provide further evidence for the reduced volumes in heteromodal association areas of ventrolateral prefrontal and lateral temporal cortices of schizophrenia patients that have long been implicated in schizophrenia pathophysiology. In addition, the present investigation adds evidence for the increased volume of recently implicated precuneus, as well as strengthens the evidence for the compromised integrity of the primary visual cortex. Present findings do not implicate medial temporal structures, thalamus, or cerebellum in schizophrenia, failing to provide evidence for the theories that proposed hippocampal complex or CCTCC circuitry to be central to understanding aetiology and pathophysiology of schizophrenia. The only sub-cortical structure found to be altered was left putamen, which was larger than normal. Finally, the present investigation was the first to compare standard and optimised VBM protocols in the same sample of schizophrenia patients, and found standard protocol to result in misregistration of the different brain tissues, raising important questions for the previous and future research.

5.4.1. Cognitive Deficits

The present investigation, in accordance with previous studies, has found that schizophrenia patients show deficits in many cognitive domains, including verbal and non-verbal learning and memory, verbal working memory, attention, executive function, verbal fluency, psychomotor processing, and speed of information processing. It is still poorly understood whether findings of the compromised function in this various domains reflect the presence of one underlying global cognitive deficit, or whether they each represent a discrete cognitive factor. If there were discrete cognitive deficits, one would expect that various cognitive deficits in patients occur both independent of each other and independent of IQ. The findings of the present investigation suggest that only fine motor function and visuo-spatial memory deficits could be explained by the

levels of general intelligence. The deficits in other cognitive functions were shown to be either completely independent or only partially related to IQ level. Further, logistic regression analyses showed that three domains, namely verbal working memory, verbal learning, and the speed of information processing (colour naming) had independently differentiated patients and controls. Krabbendam and co-workers (2001) have identified these three domains as familial cognitive risk factors in schizophrenia. They assessed neuropsychological function in schizophrenia patients, their first-degree relatives, and normal controls and found that speed of information processing, working memory, and episodic memory independently discriminated patients and their unaffected relatives from normal controls, with the degree of the impairment having a different order of magnitude in patients and their relatives. Therefore, these domains might represent cognitive vulnerability indicators underlined by genetic mechanisms. If future studies were to confirm the findings of Krabbendam et al. and the present investigation in singling out these cognitive domains as signatures of schizophrenia, this potentially may lead to the development of better screening for prodromal cases and preventive strategies, reducing the incidence rates and improving outcome in individuals vulnerable for schizophrenia. Furthermore, Lewis (2004) has argued that cognitive dysfunction should be included as a diagnostic criterion for schizophrenia. Tsuang et al. (2002a, 2002b) proposed including a new category of "schizotaxia" in the next addition of the DSM, which is defined as a state of vulnerability or predisposition to develop schizophrenia. They proposed that DSM criteria for such a category would incorporate biological and neuropsychological abnormalities. The results of the present investigation showed that the deficits in verbal learning and memory, working memory and speed of information processing correctly predicted 31 out of 33 or 94% of schizophrenia patients. Lewis (2004) argued that the inclusion of the cognitive criterion may "enhance the predictive utility of the existing non-specific DSV criteria for schizophrenia, particularly in early psychosis, in which it is so difficult to make the diagnosis based purely on psychotic symptoms and impairment of functioning" (p.110). Indeed, two subjects from the patient group who were misclassified (using linear regression) as 'normal controls' were first episode psychosis patients, who did not present with as severe deficits of working memory, verbal learning and memory, and the speed of information processing as other two first-episode or chronic patients. Future studies should evaluate the specificity of these cognitive impairments to schizophrenia by i) cross-sectionally comparing schizophrenia patients with those holding different psychiatric diagnoses, particularly affective disorders; and ii) longitudinally assessing whether first-episode psychosis patients with and without these cognitive deficits

subsequently receive schizophrenia or 'lighter' diagnosis. If reliability and diagnostic specificity of this triad of neuropsychological abnormalities were to be established by future research, its inclusion as a criterion for schizophrenia might indeed prove useful for the diagnosis and prevention.

5.4.2. Structure/Cognition Relationship

Supporting the conclusion of the review of the structure/function relationship (Chapter 2, Antonova et al., 2004) and the hypothesis of study 7, the findings of the present investigation showed that global structural alterations tend to associate with global cognitive deficits such as IQ and specific cognitive deficits that were not independent of IQ levels, whereas regional structural alterations tend to associate with specific cognitive deficits, that are wholly or partially independent of IQ levels. This pattern of associations makes good theoretical sense and suggests that the wide spectrum of cognitive deficits in schizophrenia cannot be simply explained by the global reduction of the brain tissue. It also argues against the notion that the deficient performance of schizophrenia patients on almost all cognitive domains can be simply explained by the generalised deficit. The data of the present thesis argue against such notion, and indicate that both hold true – i.e. specific cognitive deficits as manifestations of alterations in specific brain regions against the background of generalised cognitive deficits as a manifestation of global brain tissue reduction.

However, the enthusiasm of this conclusion is dampened by the fact that although some specific structure/function associations were found, generally there was a relative lack of associations between structural alterations and cognitive deficits. Noticeably, the pattern of cognitive deficits is more diverse than the pattern of structural alterations identified in the present cohort. Cognitive deficits of verbal working memory, sustained and selective attention, perseveration, visuo-spatial memory, and psychomotor speed did not associate with any of the structural alterations. It is possible that individual patients have alterations in different 'nodes' constituting the functional neural systems associated with these cognitive processes, making it impossible to identify the 'source' of these deficits at the group level. Alternatively, cognitive deficits might result due to the abnormal neurochemical transmission (this is more likely given the improvement with atypical antipsychotics and rather subtle and heterogenous stuctural alterations in schizophrenia) and/or altered effective connectivity between different brain regions. Future studies should combine functional and structural MRI as well as receptor imaging methods for the study of cognitive

dysfunction in schizophrenia to disentangle these possibilities. Finally, the present investigation assumed linear relationship between structural alterations and cognitive deficits, which might not necessarily be the case. Future studies should investigate the possibility of more complex relationship between structural alterations and cognitive functioning in both affected and unaffected individuals.

One of the most intriguing conclusions from the review of the structure/cognition relationship in schizophrenia presented in *Chapter 2* (also see Antonova et al., 2004) was that structure/cognition relationship might be altered in schizophrenia patients. This conclusion was tentative since no previous research has formally investigated the differences in structure/cognition associations between patients and normal controls. *Study 3* of the present thesis has directly tested the hypothesis that structure/cognition relationship is altered in schizophrenia and has found dissociation between patients and controls in the relationship between brain structure and learning & memory. This finding is interesting on the following account. Functional imaging studies, using PET and fMRI, have repeatedly found that schizophrenia patients underactivate brain areas that are active in controls, but also activate alternative brain areas, usually called by the researchers 'compensatory', during performance of various cognitive tasks. For example, Wiser and co-workers (1998) found that although schizophrenia patients and controls reached a similar level of performance on a word recognition task, they appeared to have achieved this goal using a different neural network. Compared to controls, patients' frontal cortex, precuneus, posterior cingulate gyrus, visual cortex and cerebellum showed less of an increase in rCBF in response to the task, whereas the anterior cingulate, the pre-and post-central gyrus, the putamen, the superior and inferior temporal gyri and the fusiform gyrus exhibited larger increases in rCBF in response to the same task. Similarly, Crespo-Facorro and co-workers (1999) observed underactivation of the left IFG, right anterior cingulate, right bilateral cerebellum in patients during recall of novel and practiced word lists, but noted an increased blood flow in the left parietal lobe during both tasks that was not observed in controls. Kim and colleagues (2003) using PET observed dorsolateral prefrontal activation in healthy subjects, and ventrolateral prefrontal activation in the schizophrenic patients during a working memory task. Further, prefrontal cortex activation in normal controls was significantly correlated with activation in the bilateral inferior parietal region, but was not correlated with any regional activation in patients. Differences in activation patterns were also reported for the relatives of schizophrenia patients relative to normal controls. Thus, Spence and colleagues (2000) conducted a PET study of obligate-carrier relatives performing a verbal fluency

task and found less functional connectivity between left PFC regions (including IFG, BA 45/47) and the precuneus, with activation in the right PFC that was not seen in normal controls. Taken together, these findings suggest that schizophrenia patients and their relatives show altered brain function relative to healthy individuals during performance of the tasks requiring higher cognitive processes.

What might explain such an alteration of brain activations in the functional studies? The findings of the present investigation suggest that the reduced volume of the structure might lead to the loss of its function. This may manifest as a reduced activation of this brain structure in functional imaging studies. Thus, the IFG volume was found to associate with learning and memory in normal controls, an association that would be expected from the data obtained by functional imaging studies. In patients, however, the IFG volume, which showed the greatest reduction, did not associate with performance on learning and memory tasks. Instead, better verbal learning in patients was associated with larger precuneus. Therefore, the underactivation in brain area in schizophrenia patients relative to healthy individuals might be due to the loss of the structural integrity in this area. Therefore, future studies of functional brain imaging in schizophrenia should correct for grey matter volume of the regions that show altered activation pattern, similarly to proposed correction for the brain atrophy for studying elderly and demented patients (Herscovitch et al., 1986; Schlageter et al., 1987).

Another novel finding of the present investigation is that the deficit in the speed of information processing measured by the tasks involving visual processing (reading colour names and naming colours) was associated with the white matter reduction of the primary visual cortex, which might include the optic radiation of the optic tract, connecting lateral geniculate nucleus of the thalamus with the primary visual areas as well as white matter fibres inter-connecting different areas of the visual cortex. This finding challenges the assumption that cognitive deficits characteristic of schizophrenia arise primarily as a result of the integration failure in the heteromodal association cortices (e.g. Pearlson et al., 1996), and points to the abnormalities earlier on in the information transfer of the sensory information to the primary sensory cortex and/or an integration of the sensory input within the primary sensory cortex (visual in this case) contributing to the cognitive dysfunction in schizophrenia.

5.4.3. Structural Alterations and Treatment Response

The investigation of the question as to whether structural alterations are predictive of treatment response with atypical antipsychotics produced more questions than answers. The present investigation was the first to address the predictive value of structural alterations in cognitive response to the atypical antipsychotic treatment. Previous research concentrated on predicting symptom improvement and found larger brain volumes to associate with greater clinical response (see *Chapter 4*). The present investigation tested the hypothesis that less alteration of structural volumes would be predictive of greater cognitive improvement with atypical antipsychotic treatment. The findings of the present investigation showed that smaller IFG and precuneus volumes were associated with greater improvement in verbal learning and memory.

One thing to note is that the relationship between the volumes of IFG and the precuneus on the one hand and verbal learning and memory on the other hand in schizophrenia patients reoccurs in different contexts in the results of the present investigation. Larger precuneus was found to be related to verbal learning at the baseline, but it was patients with smaller precuneus who benefited most from the atypical antipsychotic treatment in terms of episodic memory function. This pattern of results could not be explained by the ceiling effect, as this possibility was refuted in the analysis of study 4 (*Chapter 8*). Moreover, patients with smaller precuneus had greater decrease in positive symptoms than patients whose precuneus was enlarged relative to normal controls. Related to that, there was a relationship between larger precuneus and the number of psychotic episodes (Study 1, *Chapter 5*). As has been speculated in the discussion of study 4, patients with larger precuneus might experience treatment resistant, with both conventional and atypical antipsychotics, psychotic symptoms leading to a greater number of acute psychotic episodes, but better episodic memory due to the increased 'vividness' of mental experiences afforded by larger precuneus. Patients with smaller, more 'normal' precuneus volume seem to benefit from atypical medication in terms of both reductions in reality distortion and improved verbal memory function. The mechanism of such action of atypical antipsychotics is not clear, since not much is known about the functional role of the precuneus and the effect of different neurotransmitters on the function of this structure.

The relationship between smaller IFG volume and greater improvement in verbal memory is difficult to explain. A few possible explanations were offered in the discussion of Study 4 (*Chapter 8*), but none were deemed satisfactory. Studies

are needed to replicate or refute this finding before an understanding can be reached.

Two other cognitive domains were found to be improved with atypical antipsychotics treatment in the present investigation, working memory and dexterity. There were no structural predictors of this improvement. Noteworthy, working memory was not predicted by any structural volumes at the baseline and did not have any structural predictors at 6 weeks, despite being a cognitive domain with the strongest differentiating power for the schizophrenia diagnosis. The improvement on working memory function was quite marked, over 1,5 sd. Most significantly from the therapeutic point of view, when differences in IQ between the patients and the controls were accounted for, patients' performance as a group did not differ from that of the control group. This suggests that although working memory is one of the most severely affected cognitive domains in schizophrenia, it can be dramatically improved by the treatment with atypical antipsychotics. This is a very encouraging finding indeed. Verbal working memory has been repeatedly found to predict occupational and independent living success in schizophrenia (review, Sharma and Antonova, 2003). Dexterity was found to predict patients with rehabilitation potential (Weaver and Brooks, 1964). The ameliorating effect of atypical antipsychotics on these functions will mean the reduction in the cost of this debilitating illness for an individual and the society. On the positive side, the fact that improvement in working memory and dexterity was not related to the severity of the structural alterations in the present investigation, at least not those that could be identified on the group level, does not limit the beneficial effects of atypical antipsychotics to patients with less severely affected neurophysiology.

An important contribution of the present investigation to schizophrenia research is the finding that cognitive improvement with atypical antipsychotics could be observed despite relatively low doses of haloperidol as a comparator. As discussed in *Chapter 8*, one of the ongoing controversies in relation to atypical superiority on cognition relative to typical antipsychotics is whether these effects can be demonstrated relative to low doses of haloperidol. The initial findings of cognitive superiority of atypical antipsychotics relative to conventional ones where challenged by the fact that low doses of typical antipsychotics do not have detrimental effects on cognitive function. Moreover, it has been shown that atypical antipsychotics display no superiority over lower doses of typical antipsychotics (Green et al., 2002; Keefe et al., 2004). The results of the present study suggest that atypical antipsychotics effect on cognition could not be simply

explained by the typical antipsychotic dose, since patients in the present study were on low doses of conventional medications, which were comparable to those used in Keefe et al. study. Neither they can be explained by the reduction in motor disorders associated with conventional antipsychotics, since, as discussed before, the motor side effect ratings were initially low and no further ascertainable change occurred. The discontinuation of anticholinergic medication might have played a role, since none of the patients required anticholinergic medication with atypical antipsychotics at 6 weeks. However, anticholinergic medication was only found to associate with LM performance in Study 2 (*Chapter 6*), but not with the tests that showed improvement in the present study. Although the present investigation cannot decisively answer the question as to whether the superior effect of atypical antipsychotics on cognitive function is due to their pharmacological properties or release from deleterious effects of conventional neuroleptics, it does show that better cognitive functioning can be achieved with atypical antipsychotics, particularly on the cognitive domains that have been consistently linked with functional outcome in schizophrenia.

9.5. Methodological Considerations

Methodological limitations of the individual studies have been listed in the discussion sections of these studies. There are, however, a few methodological considerations that limit overall generalisability of the findings of the present investigation. First, the sample of schizophrenia patients recruited for the studies consisted of predominantly paranoid patients; therefore, the present findings might not apply to other clinical sub-types. In addition, most patients were living in the community and thus relatively well functioning, which limits the generalisability of the present findings to the patients with relatively good outcome.

Second, the possibility that there might be gender differences in the pattern of structural alterations and the relationship of these alterations to cognitive deficits and treatment response cannot be excluded. The sample size was not large enough to allow separate analyses for male and female patients. However, gender was controlled for in all analyses. Therefore, the observations reported in this thesis are applicable to schizophrenia patients regardless of gender.

Third, the groups were not perfectly matched on all demographic criteria, such as age. However, confounding effects of age were controlled for by performing ANCOVAs.

Fourth, subtle abnormalities in cellular orientation, structural connectivity, receptor distribution and sensitivity, and neurotransmitter distribution, among other factors, are not detectable by MRI. Therefore, the power to identify structural alterations in the present cohort was limited by the chosen method of study, with all the obvious limitation for the rest of the findings. For example, cellular and neurotransmitter abnormalities that have been reported in the DLPFC, hippocampus, thalamus, anterior cingulate and other brain regions of schizophrenia patients could not be detected using methods utilised in the present investigation. Furthermore, the VBM may not detect very small grey matter reductions, grey matter reductions in areas of high variability in grey matter volume, or grey matter recutions with an inconsistent location, leading to type 2 errors. The structural alterations identified in the present investigation should be viewed as regional differences representing foci of maximal change, rather than regions that are exclusively or selectively affected. Therefore, there might be structural abnormalities that have a relationship to cognitive deficits in the present cohort of paitents, but could not be identified in the present investigation due to methodological limitations.

A final issue concernes the assumption that structure/function relationship can be studied using standard neuropsychological tests. Since these tests were developed for the assessment of cognitive disturbances occurring due to brain lesions of either surgical or organic origin that tend to be quite extensive and generally involve several cognitive processes interacting with each other for the optimal task performance, it might be unreasonable to expect that they can be 'mapped' accurately onto brain volumes with high spatial resolution as allowed with VBM. The future challenge lies in developing tests that might be more adequate for addressing research question posited by the present investigation.

9.6. Future Directions

The present thesis has identified a number of research questions for future investigations. Most intriguingly, present data suggest an emerging role of the precuneus in schizophrenia. This structure has not been previously considered in

theoretical accounts of schizophrenia pathology, and neglected by the ROI studies. It has only recently been implicated as a site of brain pathology in schizophrenia using VBM method, with increased availability of grey matter (however, Shapleske et al (2002) have found a decrease). The findings of the present investigation implicate the increased volume of the left precuneus as having a beneficial effect on verbal memory and learning in schizophrenia, the function that is most severely affected in the majority of the patients. Furthermore, increased volume of the precuneus appears to be related to the recurrent form of psychotic symptoms as well as treatment response with atypical antipsychotics. Yet, the role of the precuneus even in normal cognition is presently poorly understood. The activation of the precuneus is noted during wide variety of cognitive functions, for example, spatial learning (Parsons et al., 2005), memory for time (Harrington et al., 2004), visual search and memory search (Makino et al., 2004), visuomotor tracking (Brown et al., 2004), and episodic memory retrieval (e.g. Mayes et al., 2004). There does not seem to be a full understanding of the conditions determining its activity. As has been discussed in *Chapter 7* (Study 3), Fletcher and co-workers (1995) advanced a unifying theory of the precuneus function, i.e. that of a mind's eye. They have shown that the precuneus is a key part of the neural substrate of visual imagery serving the purpose of episodic memory retrieval. If this theory is correct, it is possible that an enlarged precuneus might manifest phenomenologically as the increased vividness of one's imagery, which can be pathologically expressed as the bluring of boundaries between what is real and what is imagined. In fact, Frith (1992) proposed that positive symptoms of schizophrenia such as hallucination, delusions of alien control, and thought insertions in patients with schizophrenia could stem from reality-monitoring deficits. Reality monitoring is defined as the discrimination between an event produced by oneself vs. external source, and the discrimination between an imagined vs. real event. Bental and Slade (1985) were first to demonstrate a relationship between hallucinations and a failure to discriminate imaged from real events in schizophrenia patients, and Rankin and O'Carroll (1995) replicated this result in healthy individuals prone to hallucinations. Frank et al. (2000) found that schizophrenia patients with auditory hallucinations had an increased tendency to report that words that had been read silently had been spoken aloud. Brebion and co-workers (2000) confirmed that patients with hallucinations and/or delusions prone to mistake mental images for perceived pictures. Interestingly, Bar et al. (2002) reported an fMRI investigation of a 53 year-old women diagnosed with schizophrenia, who showed elevated activity in medial parietal area, overlapping with precuneus, when experiencing tactile hallucinations, but not when similar tactile stimulation was applied to her

body by the experimenter. Therefore, it is possible that the role of the precuneus in hallucinatory experiences might arise due to it being a part of a network important for monitoring agency, i.e. whether actions are self-produced or generated by others. Enlarged precuneus might lead to reality-monitoring failures by producing an abnormal salience of imagined content (possibly independent of modality, as data seem to suggest). Abnormal precuneus might also be related to another positive symptom, formal thought disorder (FTD), since Erkworth et al. (2002) have observed significant activation in the right precuneus in patients with positive, but not negative, FTD during selective attention task using PET. The authors have speculated that schizophrenia patients with positive FTD may rely on the encoding process ascribed to the precuneus (comparison and response selection via the use of imagery). Further supporting the link between precuneus, positive symptoms, and memory, Kindermann and colleagues (2004) have recently observed that schizophrenia patients with more positive symptoms on the PANSS showed greater activation during spatial memory task in the right precuneus. It is also known that patients with predominantly positive symptoms, i.e. of paranoid type, show less severe impairment on the tests of episodic memory (review, Zalewsky et al., 1998). Finally, there is evidence suggesting that overactived precuneus is associated with the disease process itself rather than mere genetic predisposition. Spence et al. (2000) have observed significantly more activated precuneus during verbal fluency task in patients with schizophrenia than either in their unaffected obligate-carrier relatives or unrelated healthy controls. The tentative link between the volume of the precuneus, positive symptoms (e.g. hallucinations, delusions, and formal thought disorder), reality monitoring, and episodic memory should be addressed in future research comparing schizophrenia patients, their obligate-carrier relatives, and individuals with schizotypy.

Future functional imaging studies will need to address the question of altered brain function in schizophrenia. In most fMRI studies using cognitive activation paradigms it is a 'peculiar' feature noted about brain function of schizophrenia patients. The brain regions activated in schizophrenia but not in controls are generally explained away as compensatory networks. It is possible that the existence of this 'altered' brain functioning might shed light on schizophrenia aetiology. Systematic investigation of the conditions under which differences in activation patterns emerge between schizophrenia patients and healthy individuals, as well as systematic investigation of the areas constituting these 'alternative' networks may lead to new insights about the nature of schizophrenia.

Future investigation of the relationship between brain pathophysiology, cognitive (dys)function, and treatment response in schizophrenia should ideally combine different MR imaging modalities, such as functional, structural and chemical shift (a type of MR spectroscopy in which spatially localised spectra are obtained using techniques derived from MR imaging), in the same cohorts of patients and with longitudinal design in order to further address the issues raised by the present investigation and to advance our understanding of this complex disorder.

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APPENDIX I

"The Relationship between Brain Structure and Neurocognition in Schizophrenia: a Selective Review"

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ADDENDUM

To reduce the multiple comparison problem in the analysis of the relationship between structural alterations and cognitive deficits performed in Study 3 (*Chapter 7*), the data were reanalysed using stepwise multiple linear regressions with cognitive deficits as dependent variables and structural alterations as independent predictors to determine which global or regional structural volume alterations were the best predictors of cognitive deficits, adjusting for age and sex. To minimize the chance of false positive errors, the predictors were considered to be significant at $p < .025$, as in Study 3. To examine the issue of altered structure/neurocognition relationship in schizophrenia, partial *r* coefficients, adjusted for age and sex, for each significant (at $p<.025$) structural predictor of a neuropsychological variable were extracted from the stepwise multiple regression analysis and contrasted between the groups using Fisher *z* transformations (Fisher 1921), as in Study 3. This method produced the same results as reported in Study 3 (*Chapter 7*).